

# **neonatal INTENSIVE CARE**

The background of the cover is an abstract geometric composition. It features a large, dark, irregular shape in the center, resembling a stylized letter 'B' or a complex organic form. This central shape is surrounded by various geometric shapes, including triangles, rectangles, and polygons, in shades of red, black, and brown. The overall effect is a high-contrast, modern, and somewhat somber aesthetic.

Vol. 24 No. 3  
May-June 2011

The Journal of Perinatology-Neonatology

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1. Centers for Disease Control and Prevention. (2003) Guidelines for Environmental Infection Control in Health-Care Facilities. Recommendations of CDC and Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR, 52(RR10):1-42.

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# neonatal INTENSIVE CARE

Vol. 24 No. 3  
May-June 2011

## Table of Contents

### DEPARTMENTS

- 4 Editorial
- 14 News
- 19 Products
- 20 Interview
- 21 PAS Preview

### ARTICLES

- 23 Breast Shield Guide
- 26 Preventing Conjunctivitis
- 28 Enteral Feeding Misconnections
- 31 "Old School" Pneumothorax
- 33 Breastfeeding and CMV
- 38 Preterm to Pre-School
- 44 C. Indologenes Infection
- 46 Hypoxic-Ischemic Encephalopathy
- 51 Reverse-End Diastolic Flow
- 54 Evidence-Based Medicine
- 59 Surfactant Assessment

## Editorial

### POINTS OF VIEW

We all know about the limits of viability and how far NICU caregivers have come in attempting to save very small preemies. But what do the preemies themselves, once they're grown up, have to say about it? How do the parents respond?

The BBC recently presented a report by Adam Wishart: "23 Week Babies: The Price of Life," in which he detailed the subsequent life of a preemie. The baby was born at 26 weeks, which was the edge of viability in 1990. Now she is a young woman of 21, and struggles with her disabilities. As she said in the article, "All I can use of my four limbs is my left arm. Without carers to lift me into my wheelchair, I'm not able to get myself anything to eat. Basically if my mother or the carers don't come, I'm stuck in bed all day." She suffers from depression. On her transition to adulthood, she said, "I had six months of counseling. I was crying every single night. I just didn't know where to turn. Horrible things were going through my head. I just wished I could end my life. There is obviously nothing else for me in my life, so what is the point of carrying on?"

Readers of the article who were themselves preemies or the parents of preemies weighed in on their experiences. A young lady said, "If you are willing to support someone at the beginning of life you should be willing to support them to the end." Another young lady noted, "I was born at 29 weeks. In 1985 this was considered to be extremely premature and my chances of survival were deemed to be quite slim. My parents were told to prepare for the worst, but the doctors continued to do everything they could for me. I struggled with health issues for the first few of years of my life as a result of being born prematurely. I am now a healthy 26-year-old woman and apart from one surgery scar I have no other signs of my early problems. I imagine that some people back in 1985 would have thought that it wasn't worth putting so much effort into such a sickly baby but I'm very glad they did."

The mother of a preemie said, "It is very challenging in terms of emotion, time and money... Keeping extremely premature babies alive at all costs is very challenging. We need to have a proper sensible debate about the whole area to avoid devastating, nasty surprises when this happens to a family. We need more than television documentaries to enable an informed debate. No one wants to even think of losing a child but when weighed against the cost of keeping them alive, and I don't mean the money, it is so all consuming. It would be kinder if we had a sensible answer that had come from informed debate, so everyone knew that children born before a certain point could be allowed a dignified exit."

A young man who is now a teacher at King's College said, "I lead a full life in spite of my disability... Provision should be improved for the disabled but the mere fact that many premature babies encounter difficulties in later life should not lead to the conclusion they shouldn't be kept alive at the outset. I was born very prematurely myself and I suffer from cerebral palsy. I cannot walk unaided. As a lecturer I feel it's safe to say that I lead a full life in spite of my disability. I can, without too much difficulty, command the attention of a room full of young and mature law students. I firmly believe that having a disability is not a hindrance in terms of attaining personal goals."

The mom of a preemie said, "Despite the enormous love I have for my son, there is not one day that I wish it had not been otherwise. He is relatively mildly affected by cerebral palsy but otherwise intellectually unimpaired. However, the first few years of his life were a nightmare of respiratory failure, emergency surgeries and now, despite surgical intervention, he will probably never walk unaided and he is one of the 'lucky' ones, a relative success story... Family life is not and never will be what it should have been and the impact on siblings is huge and life-long."

Another reader responded, "Should we be sustaining life if we do not have the resources to cope with the often devastating impact of prematurity further down the

*Continued on page 22...*



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## BIOMED CENTRAL NEWS

To further promote Open Data and data sharing, BMC Research Notes has launched a series of articles on data standardization, sharing and publication. BioMed Central is looking for contributions from all fields of biology and medicine. The timely launch of this collection coincides with a themed issue in Science exploring data sharing for biomedical and clinical research that highlights articles from Trials and BMC Bioinformatics. The Scientist magazine also recently emphasized the importance of data standards. Contact [biomedcentral.com](http://biomedcentral.com).

## PLACENTA & BRAINS

Researchers at the University of Southampton have found evidence linking brain function variations between the left and right sides of the brain to size at birth and the weight of the placenta. Children who were born small, with large placentas, showed more activity on the right side of their brains than

the left. It is this pattern of brain activity that has been linked with mood disorders such as depression. The study adds to a growing body of evidence showing that adverse environments experienced by fetuses during pregnancy (indicated by smaller birth size and larger placental size) can cause long-term changes in the function of the brain. The neurological responses of 140 children from Southampton, aged between eight and nine, were monitored for the study. Tests evaluated blood flow to the brain in response to increased brain activity, exposing differences in the activity of the two sides. Researchers measured tiny fluctuations in the temperature of the tympanic membrane in each ear, which indicate blood flow into different parts of the brain. Disproportionate growth of the placenta and the fetus is thought to occur in pregnancies where the mother has been experiencing stress or where she hasn't received sufficient nutrients.

## WEAK MILK

A study conducted at the University of Granada and at the University Hospital San Cecilio revealed that preemie mothers' milk contains low concentrations of coenzyme Q10, which is an antioxidant and a component of the electron transport train. The study examined the presence of Q10, as well as its concentration in colostrum, transitional, and mature milk. Researchers selected 30 nursing mothers, 15 who had completed their gestation and 15 moms of preemies. Milk samples were taken and moms completed questionnaires about their eating habits. The study revealed colostrum CoQ10 concentrations of about 0.4  $\mu\text{mol/l}$  in preterm mothers and 0.7  $\mu\text{mol/l}$  in term mothers. As such, CoQ10 concentrations in mothers at term are 75% higher than in preterm mothers.

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NEONATAL INTENSIVE CARE has been providing vital information to neonatal caregivers for two decades. Our readers are healthcare professionals in the fields of neonatology and perinatology, respiratory therapy, fetal medicine and research, neonatal nursing, NICU management, neonatal pharmacology, neonatal pharmacology, and obstetrics and gynecology. The scope of each issue includes clinical studies, product reviews, diagnostic techniques, modalities of care, facility reports, management issues, product reports, the latest about ethical issues, and relevant case studies. We also feature guest commentaries and works in progress, letters, news, interviews, and any information of interest to neonatology practitioners.

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## SWIRL AND SPIT

Research funded by Pennsylvania and P&G showed that use of non-alcohol antibacterial mouth-rinse containing cetylpyridinium chloride (CPC) decreases the incidence of preterm birth. Researchers studied 204 pregnant women at 6-20 weeks gestation with periodontal disease. One hundred fifty-five served as untreated controls and 49 received antimicrobial Crest mouthrinse. Dental exams were performed at baseline and prior to delivery. There was no significant difference at baseline in smoking, prior preterm birth or alcohol consumption between groups. Maternal age was higher in the rinse group than in the control group. No adverse events were observed. The incidence of PTB less than 35 weeks was significantly lower in the subjects using the rinse compared to the controls. Gestational age and birth weight (adjusted for maternal age) were significantly higher in the rinse group.

## DEADLY TREATMENT

The FDA said terbutaline administered by injection or through an infusion pump shouldn't be used in pregnant women for prevention or prolonged treatment of preterm labor due to the potential for serious maternal heart problems and death, and that oral terbutaline tablets should not be used for prevention or treatment of preterm labor. Terbutaline is used to treat bronchospasm associated with asthma, bronchitis, and emphysema. The drug is used off-label for obstetric purposes, including treating preterm labor and uterine hyperstimulation. Terbutaline has also been used in an attempt to prevent recurrent preterm labor. There is no evidence, according to the FDA, that use of terbutaline to prevent preterm labor improves infant outcomes. The FDA noted its awareness that administration of

terbutaline by injection to pregnant women occurs in hospital settings in certain urgent situations. The FDA warning relates to safety concerns about the prolonged use of terbutaline injection beyond 48-72 hours. Only generic versions of the drug are currently available.

## BUDDY SYSTEM

Women who go into labor with a companion are less likely than women going it alone to have a safe uneventful birth experience, according to a study by The Cochrane Collaboration. Cochrane studied 15,061 women who participated in 21 randomized controlled trials. Women who received supportive care from a companion throughout labor were less likely than women without such support to have a cesarean section, to use narcotics or any other pain medication, to use epidural analgesia, to give birth with vacuum extraction or forceps, and to rate their childbirth experience poorly. Having continuous support also shortened labor, and also decreased the chance of a baby having a poor Apgar score. Women receiving support were 28% less likely to have a c-section, 31% less likely to use oxytocin to hurry labor, 9% less likely to use pain meds and 34% less likely to rate their childbirth as a negative experience.

## HOW IT WORKS

The following note appeared in the latest issue of The Placebo Journal ([placebojournal.com](http://placebojournal.com)). The editor wrote: I have for some years written that society has broken its compact with physicians and in so doing has altered their actual role. The utter consumption of medicine by the third-party payer mentality, and the expectation of perfect care to be enforced by lawyer-threats made physicians largely a commodity; once patients



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were granted healthcare as a right by their elected officials, that finished the transformation. Through the onerous sanctioning of state, federal, and quasi-governmental institutions, the work of doctors has become largely the property of the state; hence, doctors have become government agents increasingly more akin to the drones at the DMV.”

### SPINA BIFIDA STUDY

A recent research study, “Management of Myelomeningocele Study,” was recently presented at the annual Society for Maternal-Fetal Medicine annual meeting. Catherine Y. Spong, MD, chief, pregnancy and perinatology branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, discussed the government study that she co-authored, which also appeared in the New England Journal of Medicine. The \$22.5 million study looked at the benefits of a surgical procedure used to repair this common defect of the spine while the baby is still in the uterus. The findings reported that the procedure greatly reduced the need to shunt fluid away from the brain. The surgical procedure consists of closing an opening at the back of the fetal spine, which is a departure from the traditional approach of operating on the infant after birth. The fetal procedure increases the chances that a child will be able to walk without crutches or other devices. The study cautioned that there were risks involved and that, because the surgery is highly specialized, it should only be undertaken in facilities with experienced staff. Infants who underwent the prenatal surgery were more likely to be born premature than were the infants who had the surgery performed after birth. Mothers who underwent the procedure were at risk of a thinning or tearing of the uterus at the incision. In spite of

these risks though, children who underwent the prenatal surgery did much better than those who had the surgery after birth. The MOMS study, which planned to enroll 200 expectant mothers carrying a child with myelomeningocele, was stopped after the enrollment of 183 women because of the benefits of the surgery.

### RADIATED

The New York Times reported on a case over-radiation of a preemie at New York Downstate Medical Center in Brooklyn. A simple chest X-ray had been ordered. Instead, the Times reported, technologists had given the baby 10 whole-body X-rays without so much as gonadal shielding. The hospital’s pediatric radiologist found that full-body X-rays of preemies had occurred often, that radiation levels on CT scanners had been set too high for infants, and that babies had been poorly positioned, making it hard for doctors to interpret the images. The Times reported that the hospital performed the so-called “babygrams” though they’d been discredited. The hospital is being investigated by state health officials. The newspaper article went on to say that errors such as at Downstate raised questions about the techs who operate radiological equipment. The American Society of Radiologic Technologists has lobbied Congress to pass a bill to establish minimum educational and certification requirements for technologists and related imaging and radiation therapy occupations, but nothing happened. Though New York State technologists are licensed through examination, there are no continuing education requirements. Information is from a report in the New York Times by Walt Bogdanich and Kristina Rebebo.

### BABY BLANKET

Neonatologists at Cedars-Sinai in Los Angeles have started using

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1. Shankaran, Seetha, et al. “Outcomes of Safety & Effectiveness in a Multicenter Randomized, Controlled Trial of Whole-Body Hypothermia for Neonatal Hypoxic-Ischemic Encephalopathy.” *Pediatrics* 122 (2008): 790-799.  
2. Zanetti, S.A., et al. “Implementation of a ‘Hypothermia for HIE’ program: 2-year experience in a single NICU.” *Journal of Perinatology* 28 (2008): 171-175.

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a new neonatal cooling blanket system to minimize brain damage in babies with hypoxic-ischemic encephalopathy. The blanket lowers the baby's body temperature to 92.3 degrees and keeps it there for 72 hours. The cooling procedure is based on research into why people who nearly drown in freezing water suffer less brain damage than other oxygen-deprived victims. The cooling slows down brain metabolism and reduces the secondary phase of damage, and the blanket gradually warms the baby's body temperature back to normal. The therapy is implemented by a specially-trained team of RNs using neuromonitoring with continuous 24-hour EEG.

## OUNCE OF PREVENTION

Intermountain Healthcare researchers found that women at high risk for preterm birth who participated in a preterm birth prevention clinic delivered more full term babies and had fewer cases of infant morbidity. Researchers conducted a retrospective review of women with a single, non-anomalous fetus and  $\geq 1$  documented previous spontaneous PTB < 35 wks. Women enrolled in a PTB Prevention Clinic were compared with women identified from a contemporary large perinatal database. Prevention Clinic patients were offered 17 alpha-hydroxyprogesterone caproate (17OHP) and were followed with serial cervical-lengths (CL); recommendations for liberal antenatal corticosteroid and tocolytic use were also made. Regular patients were managed by their primary obstetrician. Two hundred and thirty-two patients (70 PTB Prevention Clinic and 162 regular patients) met inclusion criteria. Groups had similar previous pregnancy characteristics. PTB Prevention Clinic patients had increased utilization of resources (including more cervical length ultrasounds and higher rates of use of prophylactic 17OHP) and delivered at later gestational ages. Rates of NICU admission were similar between groups (44.3% vs 40.7%,  $p=0.62$ ). However, rates of major neonatal morbidity (diagnosis of NEC, BPD, IVH, sepsis, or death) were lower among PTB Prevention Clinic neonates (5.3% vs 15.4%,  $p=0.025$ ). The study showed that among this high-risk population, referral to a consultative PTB Prevention Clinic (with standardized counseling, management recommendations, and close surveillance) resulted in a reduction in the rate of recurrent PTB prior to 37 weeks, led to an average of a one week longer pregnancy, and reduced the rates of major neonatal morbidity.

## OFF-LABEL SUCCESS

The Wall Street Journal reported on an inexpensive drug therapy that surpassed conventional laser procedures for fixing ROP in preemies, according to a study at the University of Texas. The New England Journal of Medicine said the 15 hospitals in the study have switched to using Avastin, injected into the eyes of newborns, instead of lasers. The drug has been used for treating cancer. An injection of Avastin stopped the blood-vessel growth inherent to ROP. The dosage to treat an infant is about

\$40. Genentech, which makes Avastin, said it doesn't promote off-label use. In the study, 150 preemies were randomized to receive Avastin or laser treatment. Retinopathy recurred in four infants treated with Avastin compared with 19 infants treated with the laser, a 20% reduction in the risk of recurrence. Among infants with zone 1 ROP, the recurrence rate was 6% with Avastin compared with 42% for laser therapy. Reported in the Wall Street Journal, from the article "Drug Shows Promise For Newborn Blindness," by Jennifer Corbett Dooren, Copyright 2011 Dow Jones & Company, Inc.

## HAND IT 2 THEM

Researchers funded by the National Institutes of Health have identified a key step in the establishment of a pregnancy. Their discovery shows how the hormone progesterone suppresses the growth of the uterus's lining so that a fertilized egg can implant in the uterus. This key step, the researchers discovered, occurs when a protein called Hand2 suppresses the chemical activity that stimulates growth of the uterine lining, also known as the uterine epithelium. At the start of each menstrual cycle, levels of the hormone estrogen begin to rise. Estrogen stimulates the cells in the uterine lining to increase in number, causing the epithelium to thicken. However, as the ovary releases an egg, levels of the hormone progesterone begin to rise. The elevated progesterone levels put the brakes on the estrogen-driven growth of the uterine epithelium. In this study, the researchers discovered that Hand2, previously found to increase in uterine cells as progesterone levels rise, is the switch that turns off estrogen's stimulating effect on the epithelium. The researchers found that exposure to progesterone halted growth of the uterine epithelium in mice with functioning genes for Hand2. However,

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despite exposure to progesterone, epithelial growth continued unchecked in the mice without Hand2 genes. The researchers also determined that estrogen stimulates the production of growth factors, which cause cells in the epithelial layer to multiply and grow. When progesterone is produced, it spurs the release of Hand2, which stops the production of growth factors. The uterine epithelial cells then stop multiplying, mature, and become receptive to the embryo.

### STILL AT RISK

Despite fetal pulmonary maturity, babies delivered at between 36 to 38 weeks still have a significantly increased risk of neonatal morbidities. To compare neonatal outcomes, researchers looked at mothers who had positive fetal lung maturity tests at between 36 to 38 completed weeks and compared the neonatal outcomes from these scheduled deliveries prior to 39 weeks with known fetal lung maturity to the outcomes from scheduled deliveries at 39 weeks to 41 completed weeks. Neonatal outcomes of women who were delivered following documented fetal pulmonary maturity at 36, 37, and 38 weeks were compared to women undergoing a scheduled delivery at 39, 40, and 41 weeks. A lamellar body count of  $\geq 36,000$ , lecithin/sphingomyelin (L/S) ratio  $>2.0$ , or a PG of 0.3 were considered mature. Neonatal outcomes examined included: NICU admission, length of stay in the NICU, total neonatal respiratory morbidity, cases of RDS, TTN, other respiratory morbidity, neonates requiring mechanical ventilation, proven sepsis, hypoglycemia, and neonatal deaths. Fetuses with major congenital anomalies were excluded. The study concluded that despite fetal pulmonary maturity, deliveries between 36 0/7 to 38 6/7 weeks are associated with significantly increased neonatal morbidity.

### AT ODDS

Many women are having different test results for Group B streptococcus GBS between their routine third trimester screening and a rapid test performed at the time of labor, according to researchers at Mass General. Women are routinely tested in their third trimester. Now, a new rapid test that returns results in approximately one hour can be administered at the time of labor. Researchers noted that two-thirds of infants with GBS sepsis are born to mothers with negative third-trimester cultures, so they wanted to see how many women with a negative GBS test in the third trimester have a positive GBS result right before delivery. The study enrolled women who presented to labor and delivery with an antepartum GBS culture. GBS cultures and rapid tests were performed during labor and compared to the third trimester GBS culture results. Among 559 women, GBS prevalence was 19.5% with the third-trimester culture and 23.8% with culture performed on samples collected during labor. Compared with the culture obtained during labor, the third-trimester culture correctly predicted GBS positivity at the time of labor only 69% of the time versus the rapid test which correctly predicted GBS positivity 91% of the time. The incidence of GBS discordance from the late third trimester to labor was 10%. African-American and Hispanic women were significantly more likely to have discordant culture results.

### PROTEIN SHAKE

Three proteins, XIAP, BID, and Bcl-2 are responsible in part for the success of progesterone treatments in the prevention of preterm labor and may also play an important role in triggering normal labor, according to researchers at Tufts. The proteins prevent preterm birth by hindering apoptosis. The study is titled "Progesterone Inhibits Basal Apoptosis In Fetal Membranes By

Altering Expression Of Both Pro- And Anti-Apoptotic Proteins," and was presented at the Society for Maternal-Fetal Medicine's Annual Meeting, "The Pregnancy Meeting."

### A NEW SPIN

The UC San Diego Health System has developed the Supporting Premature Infant Nutrition (SPIN) program to help mothers produce sufficient breast milk for their premature infants. The program is now available on line. With a new website and online educational videos, SPIN is ready to broaden its awareness to mothers, fathers and families beyond the UC San Diego Health System. The site has a variety of patient resources, such as pumping log sheets, milk recipes, lactation research and publications. The online tools allow mothers to learn about the program and follow the steps at their own convenience. Since not all hospitals will let mothers and their premature babies have skin-to-skin contact, the videos can also serve as a teaching model for other health institutions and patients. SPIN's goal is to improve the manner in which neonatal intensive care units across the nation support optimal nutrition and growth to premature infants. Contact [spinprogram.ucsd.edu](http://spinprogram.ucsd.edu).

### HORMONES FOR TWINS

Researcher C. Andrew Combs and colleagues conducted a placebo-controlled, double-blind, multicenter, randomized clinical trial where mothers with diamniotic/dichorionic twins were randomized to 17-alpha-hydroxyprogesterone caproate (17P) (250 mg IM) or placebo (castor oil vehicle, 1 mL), starting at 16-23 weeks gestational age (GA), repeated weekly until 34 weeks GA. A sample size of 240 mothers (480 babies) was calculated to give 80% power to detect reduction of composite neonatal morbidity from 45% with placebo to 30% with 17P. One hundred and sixty mothers were randomized to 17P, 80 to placebo at mean GA of 20 weeks. The results showed that baseline characteristics were similar between the groups. There was no significant difference in composite neonatal morbidity (14% with 17P vs 12% with placebo), or in mean GA at delivery (35.3 wks vs 35.9 wks), delivery  $< 28$  wks (2% vs 1%),  $< 32$  wks (9% vs 5%),  $< 35$  wks (33% vs 26%). There were no perinatal deaths in the 17P group and three neonatal deaths in the placebo group, two after withdrawal of life support because of fetal anomalies not discovered prenatally and one attributed to neonatal sepsis. The study concluded that the use of 17P in twin pregnancies did not reduce the rate of preterm delivery or neonatal morbidity.

### TOO MUCH CALCIUM

Researchers at Yale School of Medicine found that excessive formation of calcium crystal deposits in the amniotic fluid may be a reason why some pregnant women suffer PPRM. The researchers investigated the idea that calcification of the fetal membranes may lead to PPRM and preterm birth. They noticed that in many women, analysis of the proteins in amniotic fluid did not show signs of inflammation. The researchers could not find any cause for their preterm birth, and wondered if calcifying nanoparticles involved in other degenerative conditions could be responsible for damage to the fetal membranes in pregnant women. The researchers used a stain to look for calcium deposits in placental and fetal membrane tissue from patients with PPRM and preterm birth, as well as full-term deliveries and used a sterile culture technique to determine whether amniotic fluid can form nanoparticles. They then exposed fetal membranes to the cultured nanoparticles to determine their ability to induce cell dysfunction, damage and cell death. The

researchers found evidence of calcification of fetal membranes collected from preterm deliveries. Fetuin, one of the major proteins involved in nanoparticle formation, was found in these deposits. Levels of fetuin in amniotic fluid were lower in women who delivered with PPROM compared to those who delivered early with intact membranes.

### **X-RAY RISKS?**

A US-UK study said clinicians should be careful about using x-rays on pregnant women and infants because of the potential for a slight increase in the risk of children developing cancer. The researchers found small increases in risk of cancer for children who had x-rays at ages less than three months and in children whose mothers had undergone an x-ray while pregnant. These increases were not statistically significant. The researchers reported no increased risk from ultrasound scans. Previous studies of children born between the 1940s and the 1970s, when radiation doses were likely to be higher, found in utero x-ray exposure to be associated with an increased risk of childhood cancer, particularly leukemia. The effect of medical radiation on young children has been less clear. Researchers compiled data on 2,690 children with cancer and 4,858 healthy children from the UK Childhood Cancer Study (UKCCS). All children were born between 1976 and 1996. A total of 305 children received 319 radiographic and related examinations while in utero and 170 children received 247 diagnostic x-ray examinations in early infancy. A total of 13,723 in utero and 138 early infant ultrasound scans were carried out. Researchers measured the risk of childhood cancer overall, and leukemia, lymphoma, and central nervous system tumors. The slightly heightened risk was found to be statistically insignificant, based on only seven cases.

### **APPROVAL**

The FDA granted approval for Makena (hydroxyprogesterone caproate injection). Makena, commonly referred to as “17P,” is the first and only FDA-approved treatment indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity. The approval of Makena was based on a study of 463 women who had experienced a previous singleton spontaneous preterm birth. The study, sponsored by the National Institutes of Health, showed that compared to controls, treatment with Makena reduced the proportion of women who delivered preterm at less than 37 weeks. After adjusting for time in the study, 7.5% of Makena-treated subjects delivered prior to 25 weeks compared to 4.7 percent of control subjects. Makena is administered via a weekly intramuscular injection beginning between 16 and 20 weeks of pregnancy and continuing until 37 completed weeks or until delivery, whichever comes first. While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth. Makena is made by the KV Pharmaceutical Company. Information above was provided by the company.

Regarding the foregoing, Think Progress reported that the cost of the preemie preventing drug Makena is being raised from \$10 per dose to \$1,500 per dose. KV Pharmaceutical of St

Louis recently won FDA approval to exclusively sell Makena last month. A spokesperson for KV said the price was worth it. But, Think Progress noted, the issue is that the price hike may deter low-income women from getting the drug. According to Massachusetts Medical deputy medical director Dr Roger Snow, “That’s a huge increase for something that can’t be costing them that much to make... For crying out loud, this is about making money.” In addition, KV sent a letter to compounding pharmacies to cease and desist from producing the drug. KV claims that because the FDA designation now makes Makena “commercially available, continuing to compound this product after FDA-approval of Makena renders the compounded product subject to FDA enforcement of violating certain provisions of the Federal Food, Drug and Cosmetic Act, as well as FDA guidance.” Thus, its privileged status now threatens companies trying to provide a cheaper version. Senator Sherrod Brown of Ohio sent a letter to KV demanding they “immediately reconsider the massive price increase.”

### **TRANSFUSIONS**

In 2010, researchers conducted a prospective use study and systematic review of published literature related to blood sample collection in ICU, NICU and PICU settings. The study was designed to assess the impact of lower-volume blood draw and the use of different size collection tubes in these settings. In the findings researchers for the first time have identified a correlation between volume of blood drawn from patients in an ICU and the incidence of transfusions. According to the findings, each ml of blood drawn from patients in the ICU increases the risk of transfusion in that patient by .2%. This is the first research study to identify a direct correlation between reduced hemoglobin levels and transfusion risk. The rate increases to .3% in PICU and NICU settings. The average ICU patient has an 8% risk of needing a transfusion because of blood draws alone. Nearly 5 million people in the US receive blood transfusions each year. According to a study in the April 2010 edition of *Transfusion*, annual expenditures on blood and transfusion-related activities for surgical patients range from \$1.62 to \$6.03 million per hospital. According to the analysis, efforts to reduce the amount of blood drawn in a blood sample can reduce the risk of “inappropriate transfusions.” In one finding, if hospitals used microtainer tubes for automated process, they could eliminate 75-93% of “inappropriate transfusions” in the ICU settings. The cost savings that the analysis showed was associated with the use of certain technologies for low volume blood sample collection.

## **PRODUCTS**

### **ILLUMINATED**

Futuremed offers its neonatal/pediatric vein illuminator, Astodia, which uses the latest technology to illuminate from underneath the target area, providing clearer resolution to help eliminate multiple punctures. The hand-held device is slim, portable, and can be slipped into a scrub shirt or lab coat pocket. It is rechargeable for consistent availability. Astodia utilizes red and yellow lights individually to accommodate different patient sizes and vein depths. The yellow light is for use with smaller patients’ veins closer to the skin surface, while the red light illuminates deeper targets. The illuminating lights are dimmable, making it ideal for use with any light source. Astodia also has a built-in time out feature to avoid possible heat issues with sensitive skin. Astodia can be used with patients weighing up to 5 kilograms. In addition to vein illumination, Astodia can be used as a

diagnostic tool for the detection of hydroceles, pneumothorax, and hydroperitoneum. It has a built in LED light source with a separate hand-held controller, allowing the healthcare professional to cradle the patient's extremity while holding the illuminator underneath the target, providing a larger illuminated target area. This also allows for diagnosis without excessive patient movement. Contact [futuremed.com](http://futuremed.com).

### CENTRICITY

The Touro Infirmary in New Orleans recently implemented GE Healthcare's Centricity Perinatal in its NICU. The site chose the scalable system as a key to further customization and to enhance the ability to implement changes quickly as patient care situations evolve. The Touro Infirmary wanted to assure complete documentation while doing away with most paper charting. Centricity Perinatal allows for concise charting options and statistical calculations and pulls data automatically. Many other hospitals have implemented the system, including facilities in Alabama, Florida, Texas, Oklahoma, and California. The system also allows physicians to review patient data from their office or home. Contact [gehealthcare.com](http://gehealthcare.com).

### STICKING TO IT

Neotech Products, Inc introduced NeoFlex Silicone Adhesive Roll, a flexible new alternative to harmful tape on fragile neonatal skin. This unique adhesive is flexible and easy to apply, adjust or remove and is great as a skin barrier. The product can be used to secure limb boards and a variety of other uses. NeoFlex is ideal for micro preemies and even older patients with sensitive skin. Conveniently packaged as a roll for single patient use, NeoFlex, like all of Neotech's products, is Latex and Phthalate (DEHP) free. Contact [neotechproducts.com](http://neotechproducts.com).

### SATISFACTION GUARANTEED

Hamilton Medical's ventilation systems have earned the top User Satisfaction Ratings in all categories in MD Buyline's Quarterly User Satisfaction Report. Hamilton Medical, Inc is entering its third year holding the top composite score in ventilation as rated by the clinical members of MD Buyline. Hamilton Medical, Inc continues to stand behind the quality of its ventilation technology products and it is passing its commitment to continued superior performance along to its customers. Beginning January 2011, all new ventilation systems purchased from Hamilton Medical, Inc have a one year labor and three year parts warranty included standard on every system. Contact [www.hamiltonmedical.com](http://www.hamiltonmedical.com), (800) 426-6331.

## INTERVIEW

### Information was provided by GE Healthcare.

The following interview was conducted by CNN, which interviewed Michael Barber, VP of Healthymagination, and Carrie Eglinton Manner, General Manager of Maternal-Infant Care for GE Healthcare.

**CNN:** The challenges presented by our nation's healthcare systems are mounting daily, and tackling these challenges will require hard work and ingenuity on the part of medical professionals at every level. To ensure that as many people as possible receive the medical care that they need is no small task, as it will require not just investment, but innovation.... GE is taking a forward-thinking approach in the healthcare arena that's changing the quality of life for people worldwide...

the Healthymagination initiative... How is GE aligning Healthymagination's business strategy with changing needs in healthcare?

**Barber:** Healthymagination is GE's \$6 billion commitment to creating better health for more people. We're doing this by developing innovations with partners across the world, really focusing on reducing the cost of care for patients, increasing access to care and improving the quality, eliminating those medical errors and inefficiencies in the system. And so we are very focused in this business strategy to help people live healthier lives, supporting customers as well as leveraging the total assets of GE to solve this big societal problem.

**CNN:** How does GE put this into practice?

**Barber:** At GE we're making several major investments into the healthcare products and we really think about the entire life of the patient from birth all the way through death. You think about aging populations, you think about what people do when they're active adults. And one of the big areas we're focused on right now is in maternal and infant care – a business that's devoted to designing and developing the much-needed healthcare solutions to mothers and infants worldwide.

**CNN:** Carrie, I understand that GE's Maternal-Infant Care has made some innovations recently. What are these innovations, and how can they make a difference in the lives of newborns?

**Eglinton Manner:** Recently, GE has expanded our Maternal-Infant Care portfolio with the Giraffe product line of infant care products—those designed for developmental care for neonates to provide a microenvironment for premature or sick babies to grow and thrive in an environment very close to the one that they left before they were born. These environments, like incubators and warmers, help provide warmth and humidity, while controlling noise and a caregiver's access to the baby—which ultimately allows for better quality of life. Our goal is to increase the quality of life for the newborns and also reduce the number of neonatal deaths.

**CNN:** What other innovations does GE's Maternal-Infant Care have in the works?

**E-M:** An innovation we're really excited about is called the Giraffe Shuttle. The Giraffe Shuttle is an accessory to GE microenvironments. It facilitates full mobility of an incubator so that babies do not need to be moved between beds during hospital transfers. About 10% of newborns require extra care after birth and are transferred from labor & delivery to neonatal intensive care. The Giraffe Shuttle reduces the potential complications associated with moving the baby that result from handling and interrupted warmth. The Giraffe Shuttle clearly helps improve the quality of care for our tiniest patients, and improving quality here directly translates to the potential to reduce healthcare costs. That is, healthier babies mean fewer infections; fewer infections mean getting out of the hospital to go home sooner. So by improving quality and reducing cost, the Giraffe Shuttle delivers GE's healthymagination promise, giving newborns the best start for a healthy life.

**CNN:** You can learn more about the advances GE is making by visiting them on the web at [GEHealthcare.com](http://GEHealthcare.com), and at [healthymagination.com](http://healthymagination.com).



## PAS PREVIEW

### Bunnell Incorporated

Booth 904

#### What products will you be featuring at PAS?

Bunnell Incorporated is celebrating 25 years in the ventilator industry. The Life Pulse High-Frequency Jet ventilator has passed the test of time. Its therapeutic flexibility makes it an indispensable tool in many NICUs. Jet pulse technology, passive exhalation, and an adjustable I:E ratio makes this high-frequency uniquely effective. The "WhisperJet" patient box with sound reduction technology is the most timely product Bunnell will feature at the 2011 PAS Conference in Denver, CO. The most recent sound reduction upgrade has lowered the sound output from 56 to 41 dB.

#### What educational/training/support materials will be available at PAS?

Bunnell has developed a three booklet pocket reference set that explains *What* high-frequency ventilation is, *Why* the Life Pulse is uniquely effective, and *How* the Life Pulse is used to care for patients. The Life Pulse HFV Training DVD will also be available at the PAS. The DVD contains a complete in-service video, a patient management video, an alarms and troubleshooting video and more. It contains everything you need to understand how the Life Pulse works and how to use it. The DVD is organized, for your convenience, into chapters so you can focus in on the information that is important to you. All these training materials and more are available on the Bunnell website at [bunl.com](http://bunl.com).

#### Why should our readers visit your display?

The number one reason neonatal clinicians should stop by the Bunnell booth is to hear how quiet HFV can be, just 41 dB. Noise in the NICU has become an important topic of research and debate. Bunnell is committed to continuous improvement and our new "WhisperJet" proves it. Stop by Booth # 904; hearing is believing. Whether you currently use HFV or not, our clinical specialists can answer all your HFV questions. Stop by and give us a try.

### Mercury Medical

Booth 629

#### What new products will you be presenting at PAS?

Mercury Medical is a leading provider of airway management products for over 45 years. At the APS/SPR meeting we will be unveiling the new Neo-Tee, the first disposable infant T-Piece resuscitator with manometer at the APS/SPR.

#### What products will you be featuring that are of particular current importance and why?

In addition to the full line of airway management products, Mercury Medical will be featuring the new Neo-Tee disposable infant T-Piece Resuscitator with built-in manometer, the air-Q infant masked laryngeal airways and Neo-StatCO<sub>2</sub><kg, the only CO<sub>2</sub> detector for babies below 1kg. The new Neo-Tee is the only disposable infant T-Piece resuscitator that is flow controlled and pressure limited offering the ability to measure more consistent, targeted Peak Inspiratory Pressure (PIP) and PEEP pressure. With the added safety features of a disposable built-in manometer, adjustable PEEP valve and Peak Inspiratory Controller it provides clinicians with an affordable

T-Piece resuscitation system that can be placed at every NICU bedside. No capital equipment allows for easy transport and the manometer offers in-line viewing of delivered pressure to the patient. Mercury Medical is also featuring infant and pediatric air-Q, the first disposable masked laryngeal airway designed for the small patient anatomy. air-Q is a rescue airway that also facilitates intubation. Clinicians can remove the connector and intubate right through the air-Q masked laryngeal airway.

#### Discuss educational /training materials you'll be promoting at the convention.

Mercury Medical offers a fully trained sales force that can fully in-service hospital departments on all of our products. In addition to detailed product brochures with specifications and product advantages, we offer product information wall posters and many of our products included instructional videos.

#### Why should PAS participants visit your display?

Mercury Medical listens to the needs of clinicians in developing new products with high quality standards. All Mercury products are designed to fulfill those clinical needs with innovative cost-efficient solutions. For example, we talked to many neonatal clinicians who were planning to implement t-piece resuscitation protocols for their NICU departments but could not afford to place expensive capital equipment at every bedside. The Neo-Tee disposable t-piece resuscitator with built-in safety features was designed in response to those clinicians who are looking for an affordable t-piece resuscitator solution. We will be happy to discuss all of our product advantages at the PAS. If attendees stop by the Mercury booth, our sales force will deliver samples of any product of interest to your facility for evaluation. Ideas for new products are always welcomed for discussion.

### NeoMed, Inc

Booth 429

#### What products will you be featuring?

NeoMed, Inc is proud to present a complete line of enteral only products specifically designed to enhance patient safety and outcomes. Our products include: Oral/Enteral Dispensers, Extension Sets, Feeding Tubes, NeoBottle, NeoDrape, SafeBaby Breast Milk Tracking System, Catheterization Trays, Urinary Drainage Kits/Catheters and Lumbar Puncture Products. Our product line features the latest clinical innovations that meet or exceed enteral safety recommendations set forth by the FDA, Joint Commission and ASPEN (American Society of Parenteral and Enteral Nutrition).

#### What educational or user training materials will be available?

NeoMed will provide clinical documentation from the FDA, Joint Commission, ASPEN, ISMP and various case studies that highlight the importance of patient safety and how our products eliminate or mitigate misconnections, mis-feeds, enteral contamination, and patient mis-identifications. NeoMed will also have a full line of products and product information sheets available to all attendees.

#### What speakers will your company be featuring?

NeoMed and SafeBaby will be sponsoring a presentation by Dr Sharon Groh-Wargo, focusing on breast milk analysis, discussing the composition of human milk between mothers and within mother's own supply.

### Why should our readers visit your display?

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*Editorial...continued from page 4*

line? ... My son was born at 23 weeks and he's now coming up to his 13th birthday. We were incredibly lucky that the doctors did everything they could to keep him alive."

One respondent noted, "It is a telling statistic - nine percent survival rate of premature babies with the very likely outcome that nearly all those will be disabled. It is complete madness for the medical establishment and society to even consider it a viable option, to artificially prolong the lives of extremely premature babies. It is a waste of resources and gives false hope. It also blights the lives of those individuals who survive. Some old fashioned blunt pragmatism is required." What do you think?



Les Plesko, Editor

Information for the above is from the BBC. Quotes have been slightly altered and/or paraphrased, and information has been edited and compressed for our readers. To see the original article, please visit the BBC by Googling the title of the article.

# Correctly Fitting Breast Shields: A Guide for Clinicians

Irene Zoppi, RN, MSN, IBCLC

As clinicians we know that breast milk is the preferred nutrition for human infants.<sup>1</sup> This is especially true for premature and immuno-compromised infants in the NICU. Research indicates that mothers' milk protects infants from prematurity-specific morbidities and their associated long-term sequelae. In fact, evidence demonstrates that the more exclusive mother's milk the infant receives over the longest period of time the greater the protection.<sup>2,3,4,5,6</sup>

In the NICU, an infants' prematurity often prohibits the ability to feed at the breast and requires mothers to find evidence-based methods for expressing their breast milk. Due to the overwhelming evidence of the protection breast milk provides, mothers of premature infants are encouraged to begin breast milk expression early after delivery. The use of a hospital-grade, double electric breast pump has been recommended for pump dependent NICU mothers in helping achieve adequate volumes of breast milk.<sup>7,8,9,10</sup>

Clinicians who work with pump dependent mothers should be knowledgeable about how a breast pump works and how to help mothers get the most milk during their pumping sessions. In this article, the importance of proper breast shield fit and its impact on milk supply is explored. This article will identify criteria for clinicians to use to assess proper fitting of breast shields, which is essential to successful breast pumping.

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Irene Zoppi currently serves as a Clinical Education Specialist for Medela, Inc. In this role, she acts as a vital resource for groups assisting breastfeeding mothers and infants. She has been frequently interviewed on radio and online regarding breastfeeding issues for mothers and clinicians. Zoppi spent many years caring for new families in antenatal, labor and delivery, postpartum and NICU settings and was involved in direct patient care and family-based education. She has extensive experience teaching in a variety of nursing education programs where she consistently received the Outstanding Lecturer title awarded by her students. She produced a video presentation on nursing students' involvement in Community Health Nursing for the National League for Nursing. Ms. Zoppi, an IBCLC since 2000 and former 1st Lieutenant in the Army Nurse Corps, has authored numerous continuing educational programs for health professionals on topics ranging from breastfeeding support to evidence-based practices on the use of human milk. She has been instrumental in developing hands-on education for clinical staff regarding breastpump technology. Irene graduated from Boston University with a master's degree in Parent Child Health Nursing and is a member of Sigma Theta Tau. This article was provided by Medela.

## How a Breast Pump Works

The function of a breast pump is to simulate the sucking action of a breastfeeding infant. This is accomplished by applying vacuum in rhythmic cycles to the mother's nipple and areola through a funnel, shaped breast shield. The breast shield is that portion of the breast pump collection kit that comes in direct contact with the mother's breast, nipple and areola areas. As the breast pump cycles, the nipple and areola are drawn into the tunnel of the breast shield by the vacuum generated from the pump. Breast milk is expressed from the breast as a result of both the vacuum (negative pressure) from the pump and the milk ejection (positive pressure) experienced by the mother. The expressed breast milk is then collected into an attached container. Milk expression by a breast pump should be comfortable and effectively drain all available milk.

## Breast Shield Fit Can Impact Mother's Milk Supply

Breast shields should be evaluated while the mother is pumping to ensure they correctly fit the mother's nipple and areola anatomy. Careful evaluation of how the mother's nipple responds as it is being drawn into the breast shield tunnel is advised. Breast shields can be either too small or too big for the mother. Breast shields that are too small may result in nipple soreness and pain, skin tissue breakdown and even excoriated nipples. As a result a mother may find pumping so painful she does not wish to continue. Any breakdown in the skin surrounding the nipples and areola may predispose the mother to develop mastitis.<sup>11</sup> Abrupt cessation of pumping may also result in mastitis. Breast shields that are too large for a mother's anatomy may cause similar skin irritation.

An incorrect fit may also result in incomplete breast emptying. Incomplete breast emptying leads to milk stasis within the breast. If milk stasis occurs, a milk protein known as the Feedback Inhibitor of Lactation (FIL) remains in the breast as well. FIL acts locally on breast tissue resulting in the down regulation of milk volume. Over time, a mother's milk supply may be critically affected leading to inadequate or decreased volume.<sup>12</sup> Ultrasound research on the lactating breast by Ramsay determined that milk ducts within the breast were easily compressible.<sup>13</sup> An ill-fitting breast shield may impede breast milk drainage by occluding the ducts also resulting in milk stasis, the presence of FIL and the eventual down regulation of a mother's milk supply.

For many years, the importance of selecting a breast shield that would fit a mother was not known. Different breast shield sizes



were limited and did not fit anatomical differences in nipple sizes. Just as mothers' breasts come in many sizes, so do their nipples. Many mothers may have experienced unnecessary pain while pumping which may have led to early cessation of breastfeeding. Manufacturers of breast pumps now provide multiple sizes of breast shields that make pumping comfortable and effective.

### Finding the Proper Fit

Knowing how to select a correct size for each pumping mother is critical to her pumping success. Visible inspection of the diameter and/or length of a mother's nipples is inadequate in determining correct breast shield sizing. The nipple is comprised of elastic tissue that is capable of stretching and elongating. During breastfeeding, a healthy infant creates oral vacuum pressures that elongate the nipple two to three times its normal resting size.<sup>14</sup> The vacuum generated by the breast pump will cause similar nipple stretching. Correct breast shield sizing, therefore can only be made by witnessing the mother while she pumps. To determine the correct breast shield fit, one must watch how the mother's nipples respond to the vacuum applied by each cycle of the pump and how her nipples are drawn into the breast shield tunnel. It is also important to ask the mother for feedback on how pumping feels to her. It may be necessary to experiment with multiple breast shield sizes to find a suitable fit.

Mothers may find that their anatomy requires the use of two different sized breast shields.<sup>14</sup> Asymmetry of paired body structures is documented within other species of animals and may result in the need for two different breast shield sizes used at the same time by the same mother.<sup>15</sup> Even when a correct fit is determined, a mother may require additional assessments over the course of her pumping history. There may be a lot of variation in what feels and looks appropriate from one day in her lactation to another. Meier et al documented pump dependant NICU mothers' need for different breast shield sizes over the course of their lactation.<sup>15</sup> As a mother progresses through lactation, the need for a different breast shield size may change.

Consider the mother who has given birth by cesarean delivery after many hours of labor with epidural anesthesia. It would not be uncommon for this mother to receive copious amounts of intravenous fluid during her labor and delivery. After delivery, the intravenous fluid exits the intracellular compartment and enters the extravascular compartment (third spacing) resulting in very edematous areas of the body. This is often seen in a mother's puffy face, swollen hands and feet, but also can exhibit as fluid collects around the nipple and areola area. This fluid shift may not be seen on the mother's first day post-partum but on subsequent days. A correctly fitted breast shield for this mother on her first day post-partum would not necessarily fit or feel comfortable on subsequent days. She would require assessment for a larger breast shield. Resizing of her breast shields may also be necessary when her milk volume increases, commonly seen on days three to five after birth. When complete diuresis of excess fluid has occurred, the mother may find her breast shield size requires resizing once again.

### The Role of Clinicians

Clinicians who work with pump dependent mothers need to be cognizant of criteria used to assure a correct breast shield fit. They should demonstrate competency in making clinical assessments regarding correct breast shield fit. These assessments are necessary interventions to ensure mothers

are pumping using appropriate products and need to be a standard of care for pump dependent mothers. Clinicians can teach mothers how to make similar essential assessments while pumping their breast milk.

### Fitting Criteria

Ensuring breast shields are correctly fitted requires knowledge of specific fitting criteria. Fitting criteria is as follows:

1. The nipple should be centered in the breast shield and move freely in the tunnel. The nipple should not rub against the sides of the breast shield tunnel. Mothers with large breasts may not be able to visualize their nipples and may require assistance to center their nipples in the breast shield. Once the vacuum of the pump starts, the mother may need to break the suction and center her nipple in the breast shield again. She may need to do this several times to achieve a good nipple position. It is also important to reinforce with the mother to be careful not to push the shields into her breast tissue when she positions or holds the shields. Ramsay's research demonstrated milk ducts and glandular tissue lie underneath the area where breast shields are positioned against the breast.<sup>13</sup> Pressing the shields "too hard" can result in damage to these ducts and glandular tissue.
2. Minimal or no areola tissue should be pulled into the tunnel. When a breast shield is correctly fitted, minimal or no areola tissue will be pulled into the tunnel of the shield. Excessive areola tissue pulled into the breast shield tunnel can also lead to tissue damage.
3. There should be gentle motion of the breast each time the pump cycles. This gentle, subtle motion suggests that the breast is getting proper stimulation while pumping. The breast seems to pulsate with each suction cycle very much like what happens when a healthy, term baby breast feeds.
4. Pumping should be comfortable. If criteria are followed pumping should feel comfortable to the mother.
5. The breasts should be well drained. The breasts should feel soft after each pumping session. They should be examined after pumping to check for areas of tenderness or areas that have not fully drained. The area not fully drained may feel firm or hard suggesting the milk duct located in that part of the breast has been inadequately drained by a potentially ill-fitting breast shield.<sup>14, 18</sup> The mother may need to pump longer or get a different size breast shield. Clinicians should explain to mothers that if they find that part of the breast is not draining, they should seek the help of a clinician or lactation consultant.

### A Helpful Teaching Tool

The use of an easily remembered acronym may help to reinforce these fitting criteria with both clinicians and pump dependent mothers. The acronym "COMFY" identifies the objective fitting criteria described in this article.

- C** – Centered nipple which moves freely in the tunnel
- O** – Only little or no areola tissue pulled into the tunnel
- M** – Motion of the breast is gentle and rhythmic with each cycle of the pump
- F** – Feels comfortable pumping
- Y** – You find a well drained breast. If an area of the breast still feels full or a bit firmer, the milk duct in that area of the breast may not be empty.

The COMFY acronym is a simple teaching tool that emphasizes criteria used to correctly fit breast shields. It is easy for both clinicians and mothers to learn and to remember. Laminated cards detailing COMFY fitting guidelines can easily be affixed to all breast pumps within the hospital setting. Clinicians can reinforce these fitting techniques whenever they are instructing mothers how to use a breast pump and mothers can easily refer to them each time they pump within the hospital setting.

## Conclusion

Clinicians can make a tremendous difference in the pumping experience of pump dependent mothers. Clinicians working in the NICU with pump dependent mothers require information on the function and use of breast pump equipment. They need to know how the pump components work together and how to ensure mothers are using correctly sized breast shields. These clinicians should know specific breast shield sizing criteria that are straightforward and can be easily interpreted and taught to mothers. Use of the acronym, **COMFY** may help clinicians and mothers understand and remember the specific criteria for a correctly fitted breast shield. Knowledge of these fitting criteria need not be complex for the clinician or for the mother.

Clinicians should demonstrate competency correctly sizing breast shields with mothers who pump breast milk. Correct breast shield sizing helps to ensure mothers will be comfortable while pumping. With this important knowledge and guidance from clinicians, mothers may be protected from injury and will be sure that their breasts are adequately emptied each time they use a breast pump.

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# Use of Alternative Modalities in Place of Erythromycin Ophthalmic Ointment for Ophthalmia Neonatorum Prevention

Aditya Badheka, MD; Julie Nagpal, MD; Arjun Nepal, MD; Benamanahalli Rajegowda, MD.

## Background

Ophthalmia neonatorum (ON) which is also known as neonatal conjunctivitis is infection of the eyes of neonates occurring within the first month, particularly the first week, of life. If the infection is not prevented and goes unrecognized and untreated, it can lead to devastating blindness in early life.<sup>1,2</sup> The causes of infection are many, from *Gonococcus* (Gc), *Chlamydia* (Chl), Herpes to other bacterial infections. In Africa, between 1,000 and 4,000 newborns are blinded by this disease annually.<sup>1,2</sup> The worldwide potential for blindness from neonatal conjunctivitis is enormous. The incidence rates range from 1.6% to 23% among the 80 million babies born annually throughout the world.<sup>1,2</sup> One of the greatest advances in the history of preventing blindness was the initiation of prophylaxis to prevent ophthalmia neonatorum. In the 19th century, the single greatest cause of blindness in European infants was gonococcus conjunctivitis and keratitis acquired at birth. Infection is acquired during delivery from infected mother with Gc/Chl infection and occasionally after delivery from genito-digital spread. In 1881, Credé introduced the application of 2% silver nitrate ophthalmic solution to the eyes of neonates at birth as a prophylaxis to prevent ON. By this method, he reduced the incidence of this disease from 8% to 0.3%.<sup>3</sup> This infection not only involves the eyes, but also causes systemic infection with scalp abrasion, vaginitis, and disseminated disease with bacteremia, arthritis or meningitis. Since the time of Credé, efforts to further improve prophylaxis have focused on the use of medications other than silver nitrate due to its lack of effectiveness against *Chlamydia*, which is now the most common cause of ON in developed countries. In addition, toxic conjunctivitis is much more commonly seen with silver nitrate use than with other medications.<sup>4</sup> Silver nitrate ophthalmic solution (1%) and tetracycline ophthalmic ointment (1%) were recommended for ON prophylaxis in the 2002 STD Treatment Guidelines, which are not available or marketed in the United States.<sup>5</sup> Routine administration of 0.5% Erythromycin Ophthalmic Ointment (EOO) immediately after birth to both eyes as a preventive measure is also recommended. However, its efficacy in preventing ON is questionable.<sup>11</sup> We hypothesized that best preventive measure to prevent ON is to identify and treat all

pregnant women along with their partner(s) before the infant is born.

## Objectives

Recently, there was a severe shortage of EOO in USA due to the change of manufacturer. The CDC, FDA, AAP have all suggested using an alternative method until further supply is made available by the manufacturer. The alternatives recommended were for the mother to be tested for Gc/Chl prior to delivery and obtaining the results as soon as possible. Alternatives were: Azithromycin Ophthalmic Solution 1%, Gentamicin Ophthalmic Ointment 0.3%, Tobramycin Ophthalmic Ointment 0.3% or Ciprofloxacin Ophthalmic Ointment 0.3%. These alternatives either were in short supply or their efficacy or resistance was not tested for Gc or Chl. These medications also produced side-effects. We hypothesized that the postnatal eye prophylaxis for ON with EOO or its alternatives is not required if careful maternal Gc/Chl status is followed during pregnancy (if mother received prenatal care) or at delivery.<sup>5</sup>

## Design and methods

The project protocol was reviewed and approved by the Institutional Review Board. All babies born at our institution, from September 1, 2009 to March 31, 2010, were candidates for the study. Babies born by vaginal delivery or cesarean section were studied. Informed verbal consent was obtained from each child's mother. Gc/Chl cultures were obtained from mothers at 35-37 weeks of gestation and if not obtained, they were cultured at time of admission and labor. EOO was administered only to newborns within one hour after birth, if mother's Gc/Chl status was unknown, equivocal or positive, or if the mother had a past history of Gc/Chl treatment. All intrapartum cultures results were followed before discharge from the hospital. The service was coordinated with OBS, bacteriology lab, neonatology service and pharmacy, which had limited supplies of EOO to administer, to only requiring infants. All maternal cultures were reviewed before the discharge of the infant and these infants were followed as outpatients.

## Results

For over 7 months, from September 1, 2009, to March 31, 2010, there were 1,397 infants from 1,392 mothers with 5 sets of twins (See Table 1). Of these, 140 newborns received EOO prophylaxis based on our criteria. Out of these 140, 94 (67.14%) were due to unknown Gc/Chl status of the mother; 30 (21.42%) due to treatment history of maternal Gc or Chl or both; and 16 (11.42%) were due to positive maternal Gc/Chl cultures at last trimester

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or at the time of delivery. Of these 16, who were positive at the time of delivery, 9 (6.42%) were only Chl positive; 3 (2.14%) were positive for both Gc and Chl; 2 (1.42%) were positive only for Gc; and the other 2 (1.42%) had equivocal results.

## Discussion

The best approach to prevent Gc/Chl infection in the infant is to identify the status of the mother and to treat her and her partner before the infant is born. Sexually transmitted diseases among pregnant women still occur despite public education, encouragement of women to seek prenatal care, and pregnancy screening for sexually transmitted diseases in early trimester. Rate of Chl infection in women of all ages ranges from 0.5% to as high as 19.4% in the United States.<sup>6</sup> Rates of Gc infection is also steadily increasing by 0.001% from 2004-2008.<sup>7</sup> The third trimester culture of GC is not routinely advocated.<sup>8</sup> Instead, in the United States, EOO prophylaxis to all infants at birth has been mandated.<sup>9</sup> Based on our seven-month study, during the shortage of 0.5% EOO, we have noticed that 16 infants (11.42%) could have been missed at late trimester or at the time of labor if the cultures were not obtained. We would have also missed the opportunity to identify mothers and their partners who require treatment. Moreover, all of these newborns received EOO prophylaxis. In this group 2 infants from mothers identified as untreated Gc required Gc prophylaxis treatment after birth. The real question about whether to culture during the last trimester or at delivery is the cost and the availability of test results within the mandated 48 hours early discharge of mother and baby. Screening for Gc/Chl, Syphilitic test, HIV test, and hepatitis test before delivery is an additional tool that not only helps identify but also to treat the mother and her partner, thereby reducing or preventing infection in the newborn infant, as shown in our study. Routine EOO prophylaxis for all infants is mandated by the law irrespective of maternal culture, type of delivery, and social economic condition. However, the EOO effectiveness has been questioned, especially in preventing Chl infection. Systemic spread of infection in the infant can occur if it is not treated.<sup>11</sup> Also, breastfeeding promoters, in this country, question the immediate use of EOO, since it interferes with early bonding and initiation of breast feeding. AAP was accommodated by the statement that EOO can be delayed until bonding and breast feeding initiation.<sup>10</sup> Based on our small study, during the shortage of EOO, screening for all pregnant women obtained at the same time of culturing for GBS between 35-37 weeks, or at time of delivery, could be the best approach to identify mothers who need treatment and newborns that need evaluation and further management. We are not condoning the use of EOO for routine eye prophylaxis, but it will not pick up the infection of the mother. Treatment of the mother for sexually transmitted diseases is equally important as prevention of the same in the newborn infant. In our institution, in addition to all Gc/Chl, culturing in the last trimester or at delivery is a standard practice. We continue to use EOO prophylaxis after establishing bonding and breast feeding initiation as a standing order. We recommend to pregnant mothers, who do not have maternal Gc/Chl cultures results in the last 4 wks of the trimester, to continue to receive EOO prophylaxis as suggested by professional organizations. Also, their cultures must be reviewed before mother and infant are discharged from the hospital, and those with positive Gc/Chl cultures should be treated. For those who have Gc culture positive reports, both newborn and mother should be treated. Mothers who have positive Chl cultures, should be treated and their newborn should be followed clinically on well-baby follow-up.

Interestingly, during the study period, there were two infants admitted to the hospital with eye infections. On the review of these cases, one infant who did not receive EOO prophylaxis had bilateral conjunctivitis due to streptococcal pneumoniae. The second infant did receive EOO prophylaxis because of unknown maternal Gc/Chl status and still presented with right conjunctivitis. Despite the positive maternal intrapartum Chl culture, the newborn's eye culture remained negative for Gc/Chl or other bacteria. Though ours is a small study in a high-risk population, it will be helpful to identify infected mother and newborn in the last trimester and soon after delivery.

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# Enteral Feeding Misconnections

Review of enteral feeding tube to IV line misconnections and a proposed solution for neonatal nutrition

## Abstract

The recognition that IV and non-IV drugs should be administered in separate devices is supported by documentation of wrong-route medication errors in medical journal articles dating back to the late 1960s. The problem of misconnections, particularly enteral feedings and breast milk being injected intravenously into neonates, still happens to this day despite warnings from virtually every affiliated professional and regulatory agency. Baxa Corporation developed the first comprehensive neonatal enteral feeding system that cannot be connected to IV lines. This paper concludes that hospitals should do a top-to-bottom assessment of whether their systems can absolutely prevent non-IV fluid tubing from being misconnected to IV lines, and take the appropriate measures to correct any deficiencies.

## Introduction

Journal articles dating back to the late 1960s and early 1970s discuss the issue of wrong-route medication errors. In the years since, many articles have been written on medical errors related to tubing misconnections. The Institute for Safe Medication Practices (ISMP),<sup>1</sup> for example, has written about oral-to-IV misconnections more than a dozen times since its inception in 1994. ISMP and other organizations have long advocated for the use of non-luer connectors for administration of any non-parenteral drugs in order to prevent the possibility of an IV infusion of a non-sterile medication. Advocates for a new standard for enteral feeding include The Joint Commission (TJC) and US Food and Drug Administration (FDA).

## Background

Historically, the nasogastric tubes used for neonatal enteral nutrition support and oral liquid medication administration have incorporated luer fittings to allow hypodermic syringes to access the tube. Although safer, non-luer tip “oral” syringes were available, their oral tips could not mate with the tubes’ luer connections. Worse yet, when a nasogastric tube was in place, a luer-tipped syringe was required for oral liquid medication and feeding administration. This scenario made it impossible to avoid the potentially devastating hazard of inadvertently misconnecting a luer-tipped syringe or bag containing a non-IV fluid to a parenteral intravenous access line.<sup>2-9</sup>

Some facilities continue to use feeding tubes with luer connections because caregivers use stock hypodermic syringes

to prepare and deliver enteral feeds. Further complicating the risk of misconnection is the fact that most common syringe-driver “smart pumps” used in neonatal intensive care units are programmed to only recognize standard hypodermic syringes.

Using standard hypodermic syringes and readily available syringe pumps is easy and cost effective. However, this solution presents misconnection risks at every step of the process.<sup>10</sup> To reduce the risk, some facilities have started adding large orange stickers to the syringes and tubes. These components are then considered “safe” simply because they are orange. The tragic reality is that the risk of a potential misconnection remains as long as there are luer-compatible connection points.

Over the past three decades, a number of manufacturers have attempted to address the issue of wrong-route administration through adapters, non-standard connectors and other individual product designs. The challenge to creating a safe enteral feeding solution is the lack of universal standards for the desired components. With the exception of the step connector (commonly referred to as a “Christmas tree” connector) used at the distal end of many adult feeding sets, there is currently no enteral standard for manufacturers to design their products to meet. The International Organization for Standardization (ISO) is in the process of developing standards for small-bore connectors on medical equipment, including enteral feeding devices.

Until this defined standard is implemented, it is difficult for manufacturers to create complementary products that they do not manufacture. For example, the companies that make the feeding tubes do not necessarily manufacture the enteral feeding pump sets, or the feeding formula containers. Therefore, one manufacturer’s connection solution may not fit with another’s.

The optimal response to the patient safety risk must account for all of the potential points of failure in the process. Any comprehensive solution must prevent practitioners from making a misconnection by adapting accessories to fit an inappropriate connection through force, or any other creative mechanism.

## Regulatory and Professional Organization Responses

Every national professional and regulatory organization involved in this issue agrees that the problem of enteral misconnections is far too common and must be solved. This position is the logical response to decades of literature documenting the risks and impact of errors, some of which are summarized in the

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references. Every alert cited represents just a fraction of the actual number of tragic and near-tragic events that have occurred with misconnections.

Prominent organizations that have positions on the enteral-to-intravenous misconnection issue are noted below.

ASPEN (American Society for Parenteral and Enteral Nutrition) has published standards for specialized nutrition support in hospitalized pediatric patients that consider the dangers of oral-to-IV misconnections.<sup>10</sup> Among their recommendations is the development of a dedicated nutrition support team to coordinate service delivery among departments and professional groups. This “nutrition support service” would be charged with developing “...performance improvement mechanisms to initiate policy, procedure, and/or protocol changes that enhance the safety and efficacy of parenteral and enteral nutrition with the goal of improving patient outcomes.”<sup>11</sup>

The FDA assembled an advisory board to establish and publish guidelines for safe enteral feeding. The first meeting was in October 2006 in Washington DC. Some of the organizations that participated included the FDA, TJC, USP, ISMP, ASPEN, ECRI, Premier Inc, Sharp, Baxa Corp, VIASYS Inc and the MD Anderson Medical Center. In July 2010 the FDA also sent a letter to enteral tubing manufacturers, healthcare professionals and hospital purchasing departments, notifying them of the FDA's concerns about luer-lock misconnections and their support of, and participation in, the development of the ISO standards referenced above.

ISMP (Institute for Safe Medication Practices) has written about oral-to-IV misconnections more than a dozen times since its inception in 1994.<sup>12-16</sup> ISMP is among the many organizations that have long advocated the use of non-luer connectors for administration of any non-parenteral drugs in order to prevent the possibility of an IV infusion of a non-sterile medication.

TJC issued a Sentinel Event Alert on April 3, 2006 warning of the significant risk posed by “tubing and catheter misconnection errors.”<sup>17</sup> TJC noted that at least six deaths were attributed to tubing misconnections and countless other near misses had likely occurred. The Alert strongly recommends that healthcare organizations not purchase non-intravenous equipment that integrates tubing connectors that can physically mate with a female luer IV line connector of any form. The Alert also clearly states that a standard luer syringe should “never” be used for oral medications or enteral feedings. The final statement of the Alert urges product manufacturers to implement “designed incompatibility” to prevent misconnections of tubes and catheters.

The Journal of Neonatal Nursing published an article that detailed implementation of an enteral nutrition and medication administration system utilizing oral syringes in the NICU.<sup>19</sup> Among the study's conclusions were that, “...converting to oral syringe delivery of medications and enteral formulas utilizing enteral-only tubing eliminated the necessity for Luer-Lok IV tubing and syringes, thereby reducing the potential for wrong-route error.”

Premier Inc published a case study that documented the collaboration between Premier, member hospitals, VIASYS Inc and Baxa Corporation to develop a new premature infant feeding

system that will keep IV lines and feeding tubes from being accidentally connected.<sup>20</sup> More information on this system is included in the following section.

Finally, tubing misconnections are an issue worldwide. The National Health Service (London), through their National Patient Safety Agency, issued a National Public Safety Alert on March 28, 2007 regarding the risks of misconnections.<sup>21</sup> The Alert was in response to 33 documented safety incidents involving oral liquids and IV administration between January 1, 2005 and May 31, 2006. This was after years of incidents that included multiple fatalities. This enteral Alert summary was simple: “Enteral feeding systems should not contain parts that can be connected to intravenous syringes, nor have end connectors that can be connected to intravenous or other parenteral lines.” The deadline for compliance with this Alert was September 30, 2007.

One consistent message resonates from all of the preceding organizations. The safest approach to eliminating the enteral-to-IV misconnection risk is to use a system that is wholly separate from all parenteral products and devices.

### **A Safe Solution**

The logical answer to preventing these wrong-route tragedies is a comprehensive, dedicated enteral system. Such a system eliminates the potential for enteral-to-IV tubing misconnection.

Baxa Corporation has provided specialty dispensers that prevent wrong-route administration since 1975. Their first product – a syringe designated for oral use only – featured a colored plunger and blue silkscreen print to distinguish it visually from hypodermic syringes. The oral syringe's specialty tip would not fit into luer connectors and, when needleless connectors were introduced into the marketplace, the Baxa devices were redesigned so they would not actuate a needleless luer connector. The Baxa product line now includes specialty syringes labeled for oral use only, enteral use only, topical use only and vaginal use only to help prevent wrong-route administration errors. The syringes are complemented by a full line of accessories that accept only the Baxa non-luer oral tip.

The most recent of the Baxa specialty devices are syringes designed only for enteral feeding. These NeoThrive Enteral Feeding Syringes<sup>23</sup> feature bold orange screenprinting and striping to distinguish them from luer syringes and other devices. As with the Baxa oral syringes, their unique tip cannot connect to a luer-needle hub, or actuate a needleless IV connector. These syringes have been designed to mate only with non-luer feeding tubes to provide a dedicated system for neonatal enteral feeding. Offered in 1, 3, 5, 10, 20, 35 and 60 mL sizes, these syringes provide a safe choice for neonatal and pediatric intensive care applications where the majority of the oral and enteral doses are provided through a nasogastric tube.

The final component in closing the loop on enteral-to-IV misconnections is a dedicated enteral syringe pump (a pump that cannot be used for intravenous infusion applications), such as the NeoThrive Enteral Pump. This specialty pump senses that a dedicated enteral syringe is seated in its driver, preventing the opportunity for intravenous infusion of enteral nutrition.

When used with a non-IV, enteral feeding tube, the NeoThrive System provides neonatal and pediatric intensive care units with a way to eliminate enteral-to-IV misconnection errors.



## Conclusion

Tubing misconnections that have allowed enteral feedings to be infused intravenously have injured, and even killed, adults and neonates for decades. Now is the time for hospitals to do a top-to-bottom assessment of what dangers exist in their own institutions and implement a solution to prevent misconnections in neonatal and other critical care settings. The NeoThrive System complies with all recommendations set by The Joint Commission on Quality and Patient Safety Position Paper.<sup>24</sup>

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# Treatment of Pneumothorax in Newborn: An Old Simple Approach Revisited

Heather Hang Duong, MD, BSc; Koravangattu Sankaran, MBBS, FRCP(c), FCCM

## Abstract

Spontaneous pneumothorax occurs as frequently as 0.7% in all newborns. A significant number of pneumothoraces resolve spontaneously with medical treatment. The management of symptomatic pneumothorax is generally with a tube thoracostomy, which at times requires mechanical ventilation resulting in prolonged hospital stay and permanent scar on the chest. Pneumothoraces can also occur as a complication of respiratory distress syndrome and/or mechanical ventilation. In such cases tube thoracostomy is routinely done further increasing hospital stay and discomfort to the neonate. However, in selected cases simple needle decompression may be all that are needed in alleviating symptoms and pneumothorax thereby reducing hospital stay, pain and scar formation. An illustrative case will be presented with detailed description of the techniques along with chest radiographs showing resolution of pneumothorax.

## Introduction

Spontaneous pneumothorax occurs as frequently as 0.7% in all newborns.<sup>1</sup> The incident is higher in infants with underlying lung conditions such as hyaline membrane disease and in infants requiring positive pressure ventilation.

It is well accepted that tube thoracostomy is required in neonates requiring ventilation because mechanical ventilation could prolong resolution and/or induce further air leak. The needle decompression is used as an emergency procedure for tension pneumothoraces while bridging placement of a traditional tube thoracotomy. Recently improvements in insertion with the Seldinger technique lead to less and less requirement for the tube thoracostomy. However needle aspiration is not generally attempted for complete resolution of pneumothorax. Further, needle aspiration technique has not been revisited in neonate since a 1978 case report by Wung et al.<sup>2</sup> The technique was performed on a 30 week old infant on positive pressure ventilation when no skilled staff was available to place a chest tube. The Verres needle (16-gauge) connected to water seal by venous tubing was placed into the 3rd intercostal space at the mid axillary line. Eventually, a tube thoracostomy replaced the needle. Obviously the intentions, equipment and techniques were different and probably caused more harm.

## Case

Our patient is a late preterm male (36 week + 5 days) admitted to the Royal University Hospital NICU for development of respiratory distress at 10 minutes of life. Mom is a 31 year old G2P1 with a medical history of essential hypertension and mild asthma. Her medication included methyldopa and intermittent use of ventolin. During this pregnancy, she had per vaginal spotting at 10-14 weeks and threatened preterm labor at 28 weeks. She is GBS positive; the rest of her serology was negative. She was induced for hypertension with artificial rupture of membrane for clear amniotic fluid. She received adequate intrapartum antibiotic coverage. Baby had nuchal cord wrapped twice which was slipped over and a true knot. Apgar score was 7 and 8 at 1 and 5 minute, respectively. He required minimal resuscitation at birth. NICU was consulted at 10 minute of life for grunting and pallor. His heart rate remained above 100 and perfusion improved after receiving a bolus of normal saline.

His initial chest X-ray revealed mild ground-glass appearance which did not warrant intubation and surfactant therapy (Fig-1). He was placed on NCPAP at +6 and 25-35% O<sub>2</sub>. Repeat chest X-ray at 24 hours of birth revealed increased opacification in the right upper lobe (Fig-2). He was placed on empiric antibiotic treatment for query pneumonia and his feed was held. Blood culture and tracheal secretions were sent and were negative for bacterial growths after 48 hours. He continued to show signs of respiratory distress - grunting, mild in drawing and nasal flaring. Repeat Chest X-ray at 36 hours of age revealed left pneumothorax and evidence of hyaline membrane disease (Fig-3). He was intubated and received a dose of surfactant. Chest decompression by needling was proposed in this case as a simple approach to pneumothorax even in a mechanically ventilated patient mostly because of the size of air leak and O<sub>2</sub> requirement.

## Technique

Equipment required for the procedure included a 23 gauge butterfly needle attached to a three way stop-cock and 20 ml syringe. The patient had already received fentanyl for intubation and thought to have adequate analgesia. He was placed in supine position exposing the side of chest where air leak was observed on the X-ray. The third intercostal space at the mid axillary junction was landmarked for site of needle insertion. Under sterile conditions the chest was cleaned with chlorhexidine. The primary operator stabilized both hands on the patient's body while driving the needle slowly through the third intercostal space above the rib. A second operator is instructed to operate the stop cock to withdraw air. Thirty-nine ml of air was removed

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Fig. 1: Chest X-ray on admission.

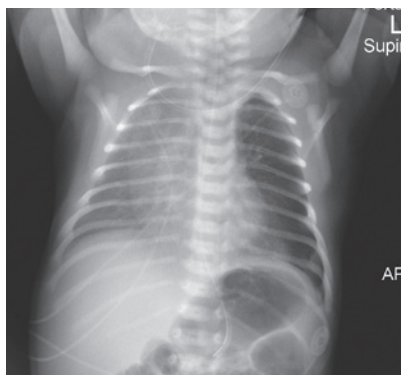


Fig. 2: Chest X-ray at day of life one.

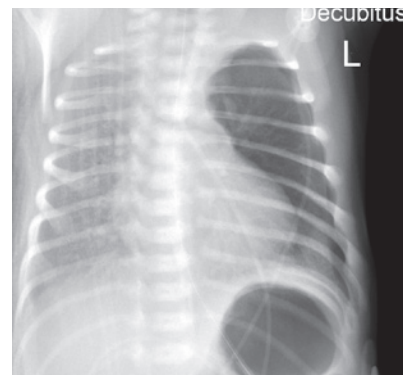


Fig. 3: Chest X-ray – lateral decubitus position. Left pneumothorax is more evident.

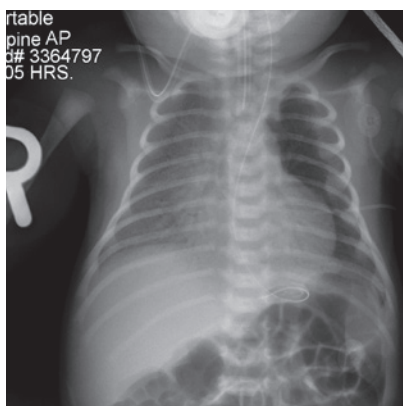


Fig. 4: Chest X-ray for visualization of residual pneumothorax.

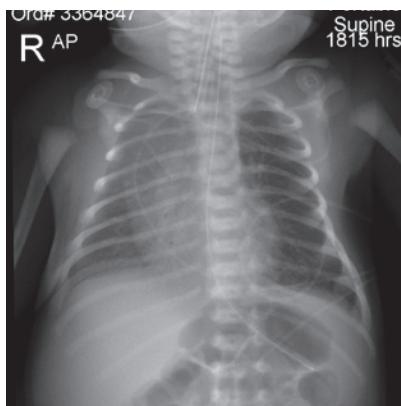


Fig. 5: Chest X-ray after 1 dose of surfactant and two needle decompressions.

from the first needle aspiration. Chest X-ray was repeated (Fig-4) revealing a smaller residual pneumothorax. A repeat needle decompression at the 2nd intercostal space mid-clavicular junction was performed and withdrew 7 ml of air.

Repeat chest X-Ray revealed complete resolution of pneumothorax (Fig-5). The patient's symptoms improved significantly. He received two more doses of surfactants and was extubated to room air on day 6. His respiratory status remained of no concerns and he was discharged home a few days later.

## Discussion

Improvement in our patient's symptoms is attributed to both administration of surfactants and relief of pneumothorax. Although chest tube thoracostomy is the recommended procedure, carries its own risks and complications. Reported complications include lung injury, phrenic nerve paralysis, chylothorax, and hemorrhagic pericardial effusion.<sup>3</sup> A study published by Litmanovitz et al reported management of pneumothorax without initial chest-tube placement in select group of ventilated neonates.<sup>3</sup> These groups of infants were more mature, were on lower ventilator setting and had better blood gases at the time of the pneumothorax. The study reported fourteen infants treated initially with needle aspiration although six received subsequent management with chest tube.

There are many advantages to needle aspiration. It is a short procedure; requires minimal instrumentation; is relatively cheap; is easy to master; causes less injury; and requires minimal

sedation and post-procedure pain management as compared to placing a chest tube and produces no scar.

Our patient's clinical status improved after needle decompression and surfactants so that he did not require a chest tube. If there is small amount of trapped air detected it can be managed with medical treatment. In selected cases needle decompression is a safe and simple alternative approach to tube thoracostomy and may avoid pain and suffering and scar.

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# Breastfeeding and Transmission of Cytomegalovirus to Preterm Infants

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## Abstract

**Background:** Breastfeeding has a major impact on CMV epidemiology. Postnatal CMV reactivation's incidence during lactation is nearby the maternal seroprevalence. Although perinatal CMV infection has practically no consequences in term newborn, it may cause, in some cases, a severe symptomatic disease in preterm newborns.

The aims of the present study are to evaluate the rate and clinical expression of CMV infection breast milk transmitted in preterm infants and to check the safety of the freezing treated breast milk.

**Methods:** The study included fifty-seven preterm infants and their CMV seropositive mothers. Fresh breast milk samples have been collected from 1st to 9th postpartum week. Both fresh breast milk and 72, 96, 120 hours frozen samples have been examined, checking the presence of CMV; urine samples have been tested too.

**Results:** 70.2% of tested mothers showed reactivation of the infection, and CMV-positive breast milk during the six weeks postpartum has been found. However, only one infant was infected by CMV, developing hepatic affection concomitantly with a multi-system involvement, as shown CMV DNA detection in urine, saliva, blood, gastric aspirate, and stools.

**Conclusion:** Freezing breast milk at -20°C and pasteurization may respectively reduce or eliminate the viral load.

## Background

Human breast milk is considered as an ideal food for newborns, both for term and preterm infants, because of its nutritional value, unique qualities and properties. However it can also be a vehicle for viral and bacterial infections, as the breastfeeding is known to have a major impact on the epidemiology of postnatal cytomegalovirus (CMV) infection.<sup>1</sup> Because of an unknown

mechanism, in women who are positive for anti-CMV IgG antibodies during breastfeeding viral reactivation can occur in the mammary glands and CMV may be generally excreted in the milk without clinical or laboratory signs of systemic infection (negative serum IgM, negative viruria).<sup>2</sup> In premature and/or low birth weight (LBW) infants, however, serious consequences may be brought by breast milk-acquired CMV infection. At the moment, premature infants who are at risk for being infected by CMV from breast milk are not guideline-filed to be identified.<sup>3,4</sup> The aim of the study is to evaluate the rate and clinical expression of CMV infection transmitted by breast milk in preterm infants, born before 32 gestational weeks and/or weighting  $\leq 2000$  g at birth, checking the safety of the freezing treated breast milk.

## Methods

**Patients:** The study has been carried out by Neonatology Intensive Care Unit (NICU) of the Teaching Hospital, in Perugia (Italy) from 1 January 2004 to 31 December 2007. Fifty seven preterm infants and their mothers, who were found CMV seropositive, were included in the prospective study. The study have been included preterm infants aged of < 32 complete weeks, or weighting < 2000 g at birth. Since the second life day, each newborn has been fed by naso-gastric tube (NGT). Peripheral blood sample has been taken from mothers after delivery, testing CMV antibodies, to determine maternal serology. CMV immunoglobulin IgG and IgM antibodies have been determined, using enzyme immunoassay kits (CMV IgG: Diamedix Miami Florida USA, CMV IgM: Diasorin Saluggia Italy).

**Microbiology:** Fresh breast milk samples have been collected from the 1th to 9th postpartum week. Fresh breast milk and 72, 96, 120 hours frozen samples have been tested, checking the presence of CMV. Milk samples have been filed and separated into cellular and aqueous fractions by centrifugation for obtaining viral isolation. CMV culture has been undertaken on aqueous fraction, using the rapid shell vial tissue culture on MRC-5 cells (Vircell, Santa Fé, Spain). After two days incubation at 37°C, the cultures have been tested checking the presence of immediate-early IE1 and IE2 (MW 68-72 kDa) CMV antigens by direct immunofluorescence, using FITC-labeled monoclonal antibodies (Chemicon Light Diagnostics, Temecula, CA, USA). Milk samples DNA have been extracted by easyMAG (bioMérieux, Marcy l'Etoile, France) as molecular tests Nested PCR has been used as screening test, and quantitative real time PCR (RT-PCR) has been used to quantify the viral DNA load (Nanogen Advanced Diagnostics s.r.l., Buttigliera Alta, Torino,

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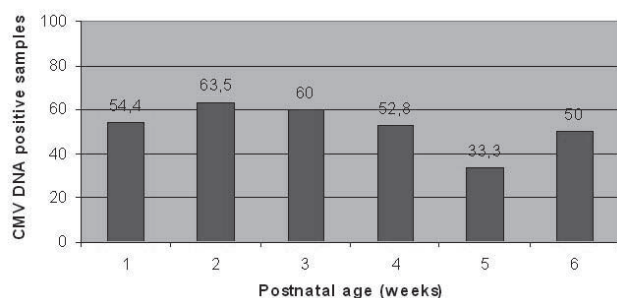


Figure 1. CMV DNA kinetics.

Italy). All samples have been assayed one by one. A negative control (distilled water) and a positive control (a DNA construct from CMV genome) have been included in each nested PCR. The lowest limit of detection was 10 copies/5 µl and 105 genomes/ml, for nested PCR and RT-PCR, respectively. Milk has been collected together with urine samples, to determine the viruria through quantitative and qualitative methods. Each infant has been fed by thawed maternal 72 hours frozen breast milk. Clinical status and laboratory tests have been documented during the study time. By informed consent, the parents of participating infants agreed them to be included in this study.

## Results

**Milk samples:** Previous viral infected mothers have been identified by IgG seropositivity towards CMV, in absence of IgM. In 40 out of 57 seropositive mothers (70.2%) the virus reactivated and was excreted in the milk during the six weeks postpartum lactation period. Maternal CMV reactivation was shown by viral shedding in breast milk (Figure 1) concomitantly with positive serum IgG but negative IgM, and negative viruria.

There was not statistically significant difference ( $p = 0.36$ ) in the values of CMV kinetics, comparing positive samples to total samples examined in the different weeks. The majority of the colostrum samples were CMV DNA positive (31 out of 57, 54.4%) and most milk samples became CMV DNA positive two weeks after delivery (33 out of 52, 63.5%). During the period of the study 109 samples were tested and the highest values of CMV DNA copies, ranging between  $10^4$  to  $10^6$  copies/mL, were shown from the 4th to the 6th week after delivery. In this period the average DNA load was  $61958.8 \pm 15818.3$  copies/mL. Thereafter, DNA copy number decreased progressively. The 72 h freezing process was capable of decreasing significantly the infectivity, as shown by viral culture, and the viral load (by approximately 75% (Figure 2). However, positive samples remained positive when tested by PCR, since viral DNA is detectable, even in the presence of very few inactivated CMV particles.

**Infants:** The average gestational age of the newborns was 29 weeks (range 23-34 weeks). The average birth weight was  $1158 \pm 436.3$  g. Among the infants who have been fed with CMV DNA-positive breast milk, only one became infected with CMV. Considering all the checked women, the rate of postnatal infection in exposed newborns was 2.5%: the rate of perinatal infection was 1.7%. The postnatal rate infection (2.5%) has been considered, because the infant became CMV positive 8 weeks after birth and the mother's serological test did not change, showing CMV IgM negative and IgG positive. This results indicate that maternal CMV reactivation was not systemic but occurred only in the breast.

All the infants were followed up to detect long-term sequelae as described for congenital and perinatal cytomegalovirus infection: each infant underwent serial monitoring (on 3<sup>rd</sup>, on 6<sup>th</sup>, on 12<sup>th</sup>, on 24<sup>th</sup>, on 36<sup>th</sup> month and on 5<sup>th</sup> of correct gestation age). To date (after at least 3 years from the enrolment), none of them presents health problems correlated with CMV infection, including the symptomatic infants.

## Case Report

The infant infected by CMV was born by cesarean section, carried out in election because of preeclampsia and intrauterine growth retardation, at 28th week and 3 days, having a birth weight of 740 g. He was initially treated for respiratory distress syndrome and hyperbilirubinemia. During the first day of life, a wide spectrum antibiotic therapy as well as Immunoglobulin IgM-enriched have been administered, because of the increasing value of C-reactive protein in absence of other clinical symptoms. However, all tests performed to detect bacterial infectious were negative: gastric aspiration and tracheobronchial aspiration, including culture test for Mycoplasma and Chlamidia, and blood culture. At age 30 days, the newborn developed conjugated hyperbilirubinemia, and the liver ultrasound showed contracted gallbladder in accordance with relevant parietal thickening. On day 47, the clinical condition of the newborn worsened: elevated serum C-reactive protein levels were found and the infant was again treated with multiple antibiotics because of a suspected sepsis, even if blood and urine cultures were negative. Cholestasis indexes worsened (Bilirubin total 14,99 mg/dL, Bilirubin conjugated 8,31 mg/dL, AST 493 U/L, ALT 183 U/L, GGT 98 U/L). Moreover, the presence of CMV DNA was evidenced in urine, saliva and blood, and of CMV-specific IgM antibodies were positive in serum. The involvement of the digestive system by CMV was confirmed by the presence of a high number of viral DNA copies detected by PCR in the gastric aspirate and stools. Congenital transmission was excluded by negative CMV DNA detection from umbilical cord and Guthrie card, even using highly sensitive real-time PCR. Clinical improvement occurred in accordance with intravenous ganciclovir therapy (7,5 mg/Kg/die twice/day for five days) followed by administration of valganciclovir (25 mg/Kg/die for six months).<sup>5</sup> The viral load gradually decreased until negativization. Molecular profiles of CMV strain isolated from infants' urine were indistinguishable from that isolated from maternal breast milk, indicating vertical CMV transmission through breast milk.

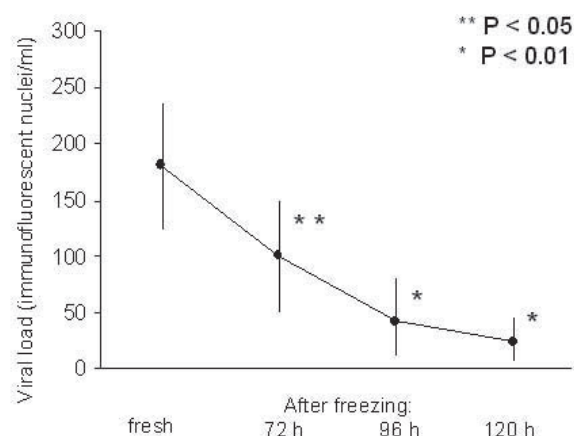


Figure 2. Load virus in milk at different time.

## Discussion

Sepsis-like syndrome in premature infants can be caused by acquired postnatal CMV infection, as reported by several studies.<sup>4,6-8</sup> In order to elucidate the role of breastfeeding in transmission of CMV infection, this study has analyzed prospectively both maternal CMV reactivation during lactation and the clinical outcome of primary infection of breastfed preterm infants. In breast milk whey CMV DNA is detectable with more reliability than in unfractionated milk or milk cells.<sup>9-12</sup> A very high proportion of CMV reactivation in longitudinally screened seropositive mothers during lactation has been found by RT-PCR, as viral DNA has been detected in breast milk from 40 out of 57 seropositive mothers (70.17%).

The mechanism of CMV reactivation in human milk, and the role of milk cells and cell-free virus in vertical transmission are still unknown.<sup>10</sup> Maternal risk factors for CMV transmission are considered to be early excretion of viral DNA and infectious virus in milk whey. The duration of breastfeeding has been related to the acquisition of CMV infection by term infants. Viral load in breast milk has not been correlated to CMV transmission. Kinetic PCR analysis performed on breast milk indicated that some samples collected during the first week after delivery were negative to CMV; viral DNA became detectable in most of the samples in the third week, but the copy number increased in the total samples examined from the 4th to the 6th week and decreased thereafter. Since the incubation time of CMV infection is between 30 and 120 days, mother-to-infant infections transmitted via breast milk should not occur until at least 6 weeks after delivery. However, more detailed studies are needed to elucidate the kinetics of CMV reactivation in the milk to reveal clearly risk factors for transmission. In only one case CMV DNA was detected in the urine 8 weeks after delivery. The newborn was not delivered vaginally, therefore he might not have acquired CMV infection from vaginal secretions during the birth process. Hamprecht et al. have reported that the transmission of CMV from breastfeeding mothers to their preterm infants could result in symptomatic CMV infections, such as sepsis-like disease, and that the early onset of symptomatic infections occurs only in extremely immature preterm infants.<sup>4,12</sup>

In a previous study, all term infants shed CMV into urine over a long period, and all of them had normal clinical courses without sequelae, but two preterm infants developed pneumonia.<sup>13</sup> Without giving sufficient evidence for breast milk as the maternal source of postnatal virus transmission, other reports have described symptomatic cytomegalovirus infection of preterm infants with clinical symptoms including neutropenia, thrombocytopenia, hepatosplenomegaly, and pneumonia.<sup>14,15</sup> In our study, we have observed CMV transmission in only 1 of 47 (2.5%) preterm infants, who had clinical symptoms related to CMV infection (sepsis-like symptoms and hepatosplenomegaly), although the viral load and detection rate (70.2%) of CMV DNA in the breast milk were high. The discrepancy between our study and other reports may not be associated with the studied population, since the mean gestational age and birth weight were similar (29 vs 29 weeks; 1158 vs 1100 g, respectively), rather with the difference in breast milk storage. In fact, before feeding, the breast milk has been kept and preserved at -20°C for 72 hours long care of in our lactarium. Hamprecht et al previously have reported that 25% of preterm infants had acquired CMV infections, after feeding with raw breast milk refrigerated at 4 to 10°C for a maximum of 12 hours.<sup>10-12</sup> CMV infections have not been observed in CMV seronegative preterm infants, fed with

banked human milk which was either pasteurized or frozen.<sup>14-17</sup> However, while detection of CMV after heating (72°C for 10 seconds) tested negative, freezing can reduce only partially CMV infectivity, especially when the virus load was high.<sup>18</sup> This may explain the occurrence of the transmission of CMV in one infant.

In conclusion, our study confirms that CMV transmission through breast milk can cause a severe clinical course in preterm infants but freezing could highly decrease the transmission rate. Because breastfeeding is healthy and wide spread, and the number of preterm infants is increasing in the most developed countries, a new procedure for gentle virus inactivation of seropositive breast milk is being assessed in our laboratory, to prevent CMV transmission to extremely preterm infants in the future.<sup>19,20</sup>

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# The Temperament of Preterm Infants in Preschool Age

Giovanna Perricone, M. Regina Morales

## Abstract

**Background:** The study deals with the characteristics of temperament of preterm infants during their preschool age in order to not only investigate likely “difficult or problematic profiles,” guided by impairments driven by their preterm birth, but also to provide guidelines for the activation of interventions of prevention, functional to improve the quality of preterm infant’s life.

**Methods:** The study involved a group of 105 children where 50 preterm children at the average age of 5 years and 2 months, enrolled in preschools of Palermo. The research planned the child reference teachers to be administered a specific questionnaire, the QUIT, made up of 60 items investigating six specific typical dimensions of temperament (Motor control activity - related to the ability of practicing motor control activity; Attention – related to the ability of guiding and keeping the focus of attention on a certain stimulus; Inhibition to novelty – regarding with emotional reactivity in front of environmental stimuli; Social orientation – meant in terms of attention and interest towards social stimuli; Positive and negative emotionality – regarding the tendency to mainly express positive or negative emotions.

**Results:** The results show in general how preschool-aged preterm infants, identified by such a study, compared with full-term children, are characterized by “normal” temperament based on a strong inclination and orientation in mainly expressing positive feelings. Yet, an impairment of the areas most relating to attention and motor control activity seems to emerge.

**Conclusions:** The data suggest specific interventions for preterm infant development and their reference systems and, at the same time, can guide paediatrician and neonatologist dealing with preterm infants, in focalizing and monitoring, even since health status assessments, specific areas of development that, since preschool age, can highlight the presence of real forerunners of

maladjustments and likely configurations of cognitive, emotional or behavior disadaptive functioning.

## Background

Premature birth is an evolutionary risk condition for children at their birth, for their survival and initial characteristics of their neonatal development (organic-functional immaturity due to gestation age - < 32 weeks, birth weight < 2000 gr, neurocognitive complications, heart and breath difficulties, muscle hypotony, poor reflexivity, etc), and, mainly, for their entire evolutionary course that it often seems to take shape even since his/her early childhood, in terms of behavior, cognitive, social and motor control impairments.<sup>1-3</sup> Several studies, in fact, highlight how preterm infants, more frequently than full-term children do, show problematic evolutionary outcomes that are often displayed at preschool and school age only. They are related with cognitive area (sensorial deficit, language impairments, learning difficulty, etc), emotional area (that is more specifically, impairments in regulation of emotions and impulses), and relational area (behavior problems and of adjustment in social relationships with their peer group and adults).<sup>4-11</sup>

This study, just referring such a heuristic picture, following the Paediatric Psychology perspective,<sup>12-15</sup> focuses its attention on some development areas of preschool-aged preterm infants. In particular, it studies the characteristics of their temperament,<sup>16-18</sup> investigating likely “difficult or problematic profiles,” guided by the impairments brought by their preterm birth and social and individual factors that interact with it, and providing guidelines to activate prevention interventions functional to the improvement of quality of life of preterm infants. They are typologies of information suggesting reference pediatricians the focuses of intervention and monitoring during health status assessments.

Therefore it can be mainly focalized specific areas of motor control development (movement coordination) or cognitive (attentive and regulative processes) or emotional (expression and modulation of emotions) that highlight, even since preschool age, the presence of real precursors of future maladjustments and likely disadaptive configurations of cognitive, emotional, maladjustment or behavior functions.<sup>9-11</sup>

In particular, the study model of reading the temperament is in terms of goodness of fit between individual and environment, meant as a variable moderating the reciprocal adjustment between child and environment<sup>19-21</sup> and referring to a series of

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**Table 1 Sample characteristics**

Characteristics of children born preterm (= 50)				Characteristics of children born full - term (= 55)		
<i>Variable</i>	<i>mean</i>	<i>ds</i>	<i>range</i>	<i>mean</i>	<i>ds</i>	<i>range</i>
Child age (months)	62	4	57-67	64	2.5	61-66
Birth Gestational Age	29	2	27-31	40	2.5	39-41
Birth Weight (g)	1800	350	1450-2400	2600	800	2300-3400
Days of Hospitalization	15	8	8-23	2	1.5	2-3
Family background of children born preterm				Family background of children born full term		
<i>Variable</i>	<i>mean</i>	<i>ds</i>	<i>range</i>	<i>mean</i>	<i>ds</i>	<i>range</i>
Age of Parents (years)	30,6	6	24-37	32,6	5	28-38
Education of parents (years)	13	8	8-23	12	8	8-22
Number children	2	1.5	1-3	2	1.5	1-4

cognitive, emotional and relational processes. Motor control activity, Attention, Inhibition to novelty, Social orientation and Emotionality are the model areas. Each of them is considered with a specific meaning.

The Motor control activity can be meant as the vigor of movement and modulation of motor control activity - the lack of such processes in preterm infants seems to guide some impairments on motor control development especially in relation to their capacity of modulating the “end” movement and visuospatial coordination.<sup>3</sup>

The Attention area is meant in terms of orientation, regulation and attention persistency, that are all processes considered, in preterm infants, little relevant by literature, at the early phases of their life mainly. Preterm infants seem to be more distractible and less able in passing and linking an emotional internal phase to an external one, monitoring what happens or their own action,<sup>22</sup> as well as they prove to be less able to keep attention focus on an object, or on what they are doing. Such unsteadiness does not seem to allow preterm infants to activate a series of mechanisms and other cognitive processes (collecting and selecting information, concentration, etc) functional to a more rational adjustment to situations.

As for the Inhibition to novelty, the model refers to emotional reactivity introducing an adjustment to social context,<sup>2</sup> under studies underlying that in preterm infants there is often a higher reactivity to external and internal stimuli than full-term children.

The Social orientation area is meant as emotional answers in front of unknown people and attention/interest towards social stimuli. Preterm infants seem to approach what is new

with a greater self-confidence than full-term children do, and show a good involvement and openness towards interpersonal relationships.<sup>17</sup>

Finally, in relation with Emotionality area, the model focalizes the predominance of negative and positive emotions referring to preterm infants' higher predisposition and orientation toward expressing positive emotions.<sup>17</sup>

Furthermore, the model states that such areas give life to profiles that, more or less characterized by the impairment of certain processes,<sup>23-26,17</sup> evolve during their development, up to reduce likely differences between preterm and full-term children. Therefore, from a social view of preterm infants as “difficult-temperament” children,<sup>19</sup> a view based on “easiness”, sociability and patience was reached.<sup>27-29,18</sup>

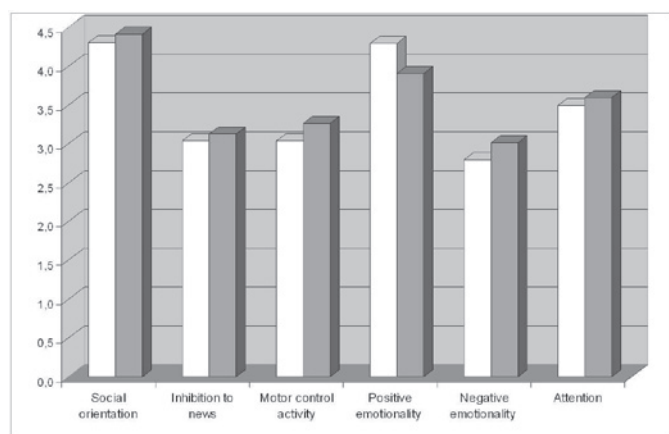
Considering the cultural contextualization of such studies, this study is aimed to verify the likely overlapping of data and then, their cross-cultural validity.

## Methods

**Objectives and hypothesis:** In light of the last considerations and in function of the above described model, the study has the following goals: Investigating the characteristics of temperament areas of preschool-aged preterm infants; Investigating the temperament profile (emotive, calm, normal, difficult) of preschool-aged preterm infants. Considering such aims, research hypothesis are to be found in: Verifying the existence of statistically significant differences between preterm infants and full-term children, with regard to the different areas defining temperament (Motor control activity, Attention, Inhibition to novelty, Social orientation and Emotionality); Verifying the

**Table 2 Temperament dimensions in preterm and full-term children**

<i>Scales</i>	<i>Mean preterm children</i>	<i>ds</i>	<i>Mean full-term children</i>	<i>ds</i>	<i>F</i>	<i>Sign.</i>
Social orientation	4,31	0,94	4,42	0,74	,496	,483
Inhibition to novelty	3,04	0,74	3,13	0,97	,253	,616
Motor control activity	3,07	1,11	3,27	1,27	,997	,320
<b>Positive emotionality (E+)</b>	4,3	0,5	3,91	0,82	7,589	,007
Negative emotionality (E-)	2,8	0,66	3,02	0,87	2,049	,155
Attention	3,5	0,82	3,6	0,87	,456	,501



**Figure 1.** Dimension of temperament in preterm and full-term children. - White: preterm children. - Gray: full-term children.

existence of statistically significant differences temperament among temperament profiles (emotive, calm, normal, difficult) of preterm infants and preschool-aged full-term children.

**Participants:** The research group (Table 1), was made up by 105 children at the average age of 5 years and 2 months. Almost every child, whose characteristics were studied, had siblings (usually 2) and belonged to families of middle social class (average one-income families where parents had an average education level of secondary school). Children, were preschool aged, and they are enrolled in schools of Palermo and province.

The involved children were divided into two groups: an experimental group, so defined because of the presence of the variable “preterm birth”, and a control group. The experimental group was made up by 50 preterm premature children, with low birth weight (mean gestational age = 29 weeks, ds = 2; mean birth weight = 1800 gr., ds = 350 gr.), selected in function of the following criteria: gestational age < 32 weeks, birthweight 1500 to 2500 gr. and lack of neurologic pathology, sensorial deficit and genetic pathology or malformative syndrome. The control group was made up by 55 full-term children (mean gestational age = 40 weeks with no pre- and perinatal complications), with the same anamnestic and sociocultural characteristics of the experimental group (cfr. Table [HYPERLINK “http://www.ijponline.net/content/37/1/4/table/T1”](http://www.ijponline.net/content/37/1/4/table/T1) <sup>1</sup>). The selection criteria of the control group were: about 40<sup>th</sup> post conceptional week at birth (range = 39-41 gestational weeks), birthweight >2500 gr., lack of pre- and perinatal complications, and lack of neurologic pathology, sensorial deficit and genetic pathology or malformative syndrome.

Every child was involved in the research after getting a declaration of approval of their parents, who were informed about aims and procedures of research path to which the study is referred, they were requested to sign a data informative, under art.13 of D.LGS. 196/2003 granting people protection and other subjects in relation to personal data treatment.

**Procedures and instruments:** A questionnaire was used to observe the behavior of children aged 3 to 6 years, belonging to the battery of Temperament Italian Questionnaires (QUIT), validated on Italian sample.<sup>21</sup>

Such a questionnaire, which can be filled in by parents (even with a low, medium-low level of education), educators and teachers, or however, anyone who, taking care children, spends his/her time with them every day, was administered to infancy school teachers that child had been attended for 3 years.

The questionnaire is structured in 60 items describing child behavior in three different contexts (child with the others; child on his play time; child facing of novelty or while s/he is performing an activity or a task), and the answers teachers can give are “almost never”<sup>1</sup> to “almost always”,<sup>6</sup> under the Likert scale. The items refer to the six areas and dimensions previously described, each explored through 10 items (Motor Control Activity items n.11, 13, 15, 16, 34, 36-40, 45, 59; Attention items 41-44, 47, 54, 57, 58; Inhibition to novelty items 26, 29, 32, 35, 48-53, 56, 60; Social Orientation items 1-10; Positive Emotionality items 12, 17, 21, 23, 25, 27, 28, 31, 46 and Negative Emotionality items 14, 18-20, 22, 24, 30, 33).

More specifically, three areas are related to child’s adjustment to environment in general: the Motor activity area, regarding the ability of performing motor activity, the Attention area regarding the ability of orienting and keeping the attention focus on a certain stimulus, and the Inhibition to novelty area related to the emotional reactivity to environmental stimuli.

The other three areas regard child’s adjustment to social world and, in particular Social orientation area is meant in terms of attention and interest in social stimuli, Positive emotionality and Negative Emotionality areas refer to the prevalence of positive or negative emotions. The last two scales of QUIT (Positive emotionality and Negative emotionality) allow to clearly assess the emotional component of temperament (“quality of mood”<sup>19</sup>), and highlight 4 temperament profiles, most consistent with Italian cultural context:

1. Emotional temperament, typical of individuals with high

**Table 3 Preterm and full-term children temperament profile**

QUIT temperament scales	mean score normative sample	ds	mean preterm children	ds	mean full-term children	ds
Social orientation	4,06	0,43	4,31	0,94	4,42	0,74
Inhibition to novelty	3,25	0,69	3,04	0,74	3,13	0,97
Motor control activity	3,66	0,46	3,07	1,11	3,27	1,27
Attention	3,82	0,72	3,5	0,82	3,6	0,87
Positive emotionality	4,03	0,52	4,3 +	0,5	3,91 -	0,82
Negative emotionality	3,37	0,58	2,8 -	0,66	3,02 -	0,87
Temperament profile typology			Normal		Calm	

emotional reactivity, who easily cry and laugh. They correspond to the definition of < < lively > >, nice and emotional child. Such a profile plan that the score obtained by the subject is higher than the mean value of the normative sample in the scale of both Positive emotionality (E+) and Negative emotionality (E-).

2. Calm temperament, typical of individuals showing a low emotional reactivity. They smile instead of laughing and get angry, cry or get frightened rarely. These children get a score lower than the mean value of the normative sample in the scale of both Positive emotionality (E+) and Negative emotionality (E-).

3. Normal temperament regarding those individuals showing a prevalence of positive emotions since the first months of their life. These children, having high positive reactivity and low negative reactivity, obtain a score higher than the mean value of the normative sample in the scale of Positive emotionality (E+) and a lower score in the scale of Negative emotionality (E-).

4. Difficult temperament, describes those individuals where negative emotions prevail against positive ones. They are children whose interactions with environment are often difficult and the child-environment adjustment is extremely problematic. They obtain a score in the scale of Negative emotionality (E-) higher than the mean value of the normative sample, while a lower score in the scale of Positive emotionality (E+).

In relation to the psychometric characteristics of the questionnaire, there is the need to specify that it was validated on a great number of subjects (n = 1533) by means of a repeated administration to both parents and child's reference teachers, performed in several Italian cities.

More specifically, as for reliability and internal validity of the questionnaire, the internal consistence of the dimensions was calculated through Cronbach's alpha, which highlighted an acceptable cohesion among QUIT dimensions ( $\alpha > .60$  in every dimensions).<sup>21</sup> Furthermore, correlational analysis was performed among the scales of the questionnaires filled in by fathers, mothers and teachers of children, by means of Pearson's correlation coefficient that highlighted the capacity of questionnaires to measure the objective aspects of temperament ( $R > .52$  e  $p < .01$ ).<sup>21</sup> Data treatment and analysis: Data codified under the procedures set by the reference test guide, were analyzed by means of the statistical program for Social Sciences - SPSS (16th version for Windows).

More specifically, in relation to the survey on likely differences between preterm and full-term children, within the different areas defining their temperament (QUIT), an analysis of one way variance (ANOVA) for continuous variables (scores related to different scales) was performed, and through Kolmogorov Smirnov's test,<sup>30</sup> it allowed to compare the sample means of preterm infant group - experimental group/preterm birth independent variable - to those of children born after a normal gestation - control group/on time birth independent variable - within the different scales of QUIT. As for the test of significance, a value of  $p = 0,05$  was used.

## Results and Discussion

The results of analysis on the differences between preterm and full-term children in the different areas of temperament, highlighted the existence of specific differences (Table 2).

Statistically speaking, preterm infants seem to significantly differ from full-term children only in the scale related to Positive emotionality ( $p < .05$ ) where they obtained a higher score than full-term children had, due to their higher predisposition toward expressing positive feelings and experiences. With regards to the other scales of QUIT (Social orientation, Inhibition to novelty, Motor control activity, Negative emotionality, Attention) preterm infants obtained lower scores compared to full-term children, even though such a difference does not have a statistic significance ( $p > .05$ ) (see Table 2; Figure 1).

Moreover, as for the possibility to assess the different temperament profiles of preterm and full-term children, a descriptive comparison between mean scores and standard deviations of preterm and full-term children and the mean score and standard deviations of the normative test sample was performed in the Negative and Positive Emotionality scales (Table 3).

In relation to the specific temperament profile, preterm infants seem to be described with a normal temperament, showing high positive reactivity and low negative reactivity (mean score in E+ is higher than mean score in E-); on the other hand, full-term children, getting a low score in both E+ and E-, show less emotional reactivity and hence, highlight a calm temperament.

The results of such a study show how preschool-aged preterm infants, compared to full-term children are characterized by a temperament profile that, within Italian culture is defined in terms of "normality" and, hence, based upon a strong predisposition and orientation toward mainly expressing positive emotions. However, although a statistical significance was not reached, preterm infants got slight lower scores in all other dimensions of temperament but in the positive emotional scale (see Table 2). So, preschool aged preterm infants involved in the research, seem to be also characterized by low levels of motor control activity, attention and negative emotive reactivity, by a predisposition toward motor and attention irregularity, and difficulty in recognizing and expressing negative emotions. Finally, preterm infants have a low score of social orientation meant as the relational curiosity functional to promote certain self-regulated answers of adjustment to external reality.

## Conclusions

Such a study, though considering the small number of the sample, highlights a temperament profile of preschool-aged preterm infants whose specificity, compared to full-term children involved in the research path, is to be found in strong predisposition and orientation toward expressing positive emotions rather than negative ones, and a high trend toward searching the other and, hence, being sociable.

Moreover, it was detected the presence of a sort of "slowness" in preterm infants involved in the research, that, even though does not reach a statistical significance, is mainly related to both motor and attention fields. So, it is to be highlighted a likely difficulty of motor control development in preschool-aged preterm infants, showing low levels of motor control activity, a less motor reactivity and difficulty of coordination and minor endurance of it.<sup>3</sup> The presence of such elements was detected by the literature in preterm infants compared to full-term children.<sup>17,18</sup>

Another aspect to be considered is related to preschool-aged



preterm infants' attention. In accordance with several studies,<sup>22</sup> a minor trend toward guiding and regulating their own attention, keeping focalization on an object, and a minor capability of moving their attention from a stimulus to another one, were highlighted. They all are processes whose impairment may be a likely risk factor for a rational adjustment to situations, and drive to difficulties in school learning.

In light of these last considerations, such a study is aimed to open new and future hypothesis on the existence of likely correlations between such temperament aspects and specific cognitive, emotive and relational functions of preterm infants. On the other side, it can guide paediatrician and neonatologist or, more generally, preterm infants cure system, in more focalizing and monitoring, within follow-up paths and related health status assessments, those cognitive, relational or motor control areas, correlated to temperament and that research data highlight in some way impaired. They are, in fact, extremely important processes for child's development,<sup>31-33</sup> so that even the little impairment of them, seems to come with specific forms of evolutionary maladjustments such as disorders and/or deficit of attention,<sup>3,22</sup> hyperactivity or disorders in emotive self-regulation,<sup>2</sup> learning<sup>34-37</sup> and language disorders<sup>38</sup> that tend to guide the preterm infants' life path in terms of "atypical" path.<sup>39</sup>

A further element that the study wants to highlight is related to cross-cultural perspective of data, that is, research preterm infants seem to be characterized by a temperament profile that, in its general configuration, can overlap to that highlighted by other studies performed on children coming from cultures deeply different from the considered one (United States, England, Australia, etc.).<sup>33,17,2</sup> More specifically, while in Italian culture, the profile of temperament dimensions is defined in terms of "normality" and hence, adaptive to the reference socio-cultural context, in other cultures it is read using different parameters and models, and therefore, interpreted in terms of "difficult" functioning, that is not functional to adjustment to reality.<sup>40-43</sup> Such a consideration, even though it does not disregard the importance of cultural attributions that guide specific temperament profiles, leads to hypothesize and question about a likely presence of a sort of "temperament syndrome"<sup>40</sup> of preterm infants, meant as the existence of a configuration of temperament of preterm infants, made up by a strong constitutional base with a cross-cultural validity. Moreover, to support such hypothesis, it could be also considered that, while other studies have detected this temperament configuration of 0-to-2-year-old preterm infants, preterm children involved in such a research are all 5 years old. So, it has been supposed the permanence of such a syndrome during the development, that would lead to define preterm infants compared to full-term children, even school-aged, in terms of emotive, sociable and patient children yet less directive, attentive and reactive to frustrations.

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# Chryseobacterium Indologenes Infection in a Newborn

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## Abstract

**Introduction:** *Chryseobacterium indologenes* is an uncommon human pathogen. Most infections have been detected in hospitalized patients with severe underlying diseases who had indwelling devices implanted. Infection caused by *C. indologenes* in a newborn has not been previously reported.

**Case presentation:** We present a case of ventilator-associated pneumonia caused by *C. indologenes* in a full-term Caucasian newborn baby boy with congenital heart disease who was successfully treated with piperacillin-tazobactam.

**Conclusion:** *C. indologenes* should be considered as a potential pathogen in newborns in the presence of invasive equipment or treatment with long-term broad-spectrum antibiotics. Appropriate choice of effective antimicrobial agents for treatment is difficult because of the unpredictability and breadth of antimicrobial resistance of these organisms, which often involves resistance to many of the antibiotics chosen empirically for serious Gram-negative infections.

## Introduction

*Chryseobacterium* spp. are Gram-negative bacilli widely distributed in soil and water. In hospital environments, they have been recovered from water systems and humid surfaces. Infections caused by *Chryseobacterium indologenes* are rare, but have been reported as a cause of serious infections in adult immunosuppressed patients. To the best of our knowledge, infection caused by *C. indologenes* in a newborn has not been previously reported.

## Case Representation

Our patient, a full-term Caucasian newborn baby boy with congenital heart disease (double-outlet right ventricle, mitral atresia and hypoplastic aortic arch) remained intubated and under mechanical ventilation from the seventh day of life due to hemodynamic deterioration. Then, 20 days later, he deteriorated clinically with worsening fever, intense leukocytosis, increase of acute-phase reactants and pulmonary infiltrate on chest radiograph. Empiric antibiotic therapy with meropenem and vancomycin was given. Bacteriological blood, cerebrospinal

fluid and urine culture test results were negative. *C. indologenes* was isolated from a tracheobronchial secretion sample obtained by endotracheal aspiration. Treatment was discontinued at 10 days on clinical improvement. Then, five days later, he again developed fever and pulmonary infiltrate on chest radiograph. *C. indologenes* was again isolated from respiratory samples obtained by bronchoalveolar lavage (BAL). No other microorganisms were isolated from the BAL sample. The bacteria were susceptible in vitro to fluoroquinolones, cefepime, piperacillin-tazobactam and co-trimoxazole with intermediate susceptibility to third-generation cephalosporins; it was resistant to meropenem, imipenem, aztreonam, sulbactam-ampicillin and aminoglycosides. Antibiotic therapy with piperacillin-tazobactam was given and continued for 14 days. Our patient continued to do well up to the time of surgery for the repair of the congenital heart disease two months later.

## Discussion

The genus *Chryseobacterium* belongs to the family Flavobacteriaceae. Six species of *Chryseobacterium* are more commonly isolated from clinical specimens: *C. meningosepticum*, *C. odoratum*, *C. multivorum*, *C. breve* and group IIb *Chryseobacterium* spp., which includes *C. indologenes* and *C. gleum*. *Chryseobacterium* spp. are Gram-negative, aerobic, non-fermentative, oxidase-positive and catalase-positive non-motile bacilli that produce a distinct yellow to orange pigment.<sup>1</sup> They are widely distributed in nature and found primarily in soil and water. They are not normally present in the human microflora.<sup>1,2</sup> They can survive in chlorinated waters, and in the hospital environment they exist in water systems and wet surfaces and serve as potential reservoirs of infection. Colonization of patients via contaminated medical devices such as respirators, endotracheal and tracheostomy tubes, humidifiers, incubators for newborns and syringes has been documented previously.<sup>2,3</sup> Contaminated surgically implanted devices such as intravascular catheters and prosthetic valves have also been reported.<sup>4</sup> *Chryseobacterium* infections in humans are usually acquired nosocomially and are frequently associated with the presence of invasive equipment (intravascular catheters, endotracheal tubes, prosthetic device) in immunocompromised patients or patients who have received long-term broad-spectrum antibiotics.<sup>4,5</sup> *C. meningosepticum* is the most pathogenic member of the genus; it is an agent of neonatal meningitis with mortality rates of up to 57% and is involved to a lesser extent in cases of pneumonia and bacterial sepsis in neonates and adults.<sup>6</sup> *C. indologenes* is an uncommon human pathogen. The clinical significance of *C. indologenes* has

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not been fully established yet because this bacterium has not been frequently recovered from clinical specimens. Reported infections include bacteremia, ventilator-associated pneumonia, indwelling device-associated infection, pyonephritis, biliary tract infection, peritonitis, lumboperitoneal shunt infection, ocular infections, and surgical and burn wound infections, and infection has been associated with a high mortality rate.<sup>4,5,7-13</sup>

In the literature we have found six cases published of infections for *C. indologenes* in children; all of the patients were older than three months of age.<sup>9-13</sup> Hsueh et al<sup>9,10</sup> reported three pediatric cases of *C. indologenes* bacteremia. The first two patients were a one-year-old girl and a five-year-old girl, both receiving chemotherapy for a neoplastic disease and both with indwelling central venous catheters. The third patient was a one-year-old boy with a burn injury who was under mechanical ventilation. The one-year-old boy with burns developed an adult respiratory syndrome and died despite antimicrobial treatment; the other two patients recovered after three days of treatment. Cascio et al<sup>11</sup> reported on a two-year-old boy with type 1 diabetes mellitus who developed bacteremia. The only medical device present was a peripheral catheter. The patient received antimicrobial treatment with ceftriaxone and recovered after two days.

In 2007, Bayraktar et al<sup>12</sup> reported on a bloodstream infection in a five-month-old baby. Molecular typing with arbitrarily primed polymerase chain reaction demonstrated the cross-contamination of commercial distillate water. The baby was infected by this water as a result of medical assistance received during hospitalization.

Al-Tatari et al<sup>13</sup> reported on a lumboperitoneal shunt infection in a 13-year-old boy with congenital hydrocephalus successfully treated with trimethoprim-sulfamethoxazole and rifampin.

To the best of our knowledge, our patient's case is the first reported example of infection caused by *C. indologenes* in a newborn. Appropriate choice of effective antimicrobial agents for treatment of infection by *C. indologenes* is difficult because of the unpredictability and breadth of antimicrobial resistance of these organisms, which often involves resistance to many of the antibiotics chosen empirically for serious Gram-negative infections.

*C. indologenes* is often resistant to extended-spectrum penicillins, first-generation and second-generation cephalosporins, ceftriaxone, aztreonam, ticarcillin-clavulanate, chloramphenicol, erythromycin, aminoglycosides, imipenem and meropenem for production of a class B carbapenem-hydrolyzing enzyme.

*C. indologenes* is usually susceptible to piperacillin alone or combined with tazobactam, ceftazidime, cefepime, fluoroquinolones, rifampin and cotrimoxazole, but the in vitro susceptibility to these antibiotics should be systematically tested.

Antimicrobial susceptibility data on *Chryseobacterium* spp. remain very limited because this pathogen has rarely been isolated from clinical specimens. The results of the evaluation of a worldwide collection indicate that the newer quinolones (garenoxacin, gatifloxacin, and levofloxacin) may represent the most appropriate antimicrobial agents to treat infections caused by this pathogen. Garenoxacin was the most active quinolone

(minimum inhibitory concentration required to inhibit the growth of 50% of organisms (MIC<sub>50</sub>): 0.12 µg/mL); gatifloxacin (MIC<sub>50</sub>: 0.25 µg/mL) and levofloxacin (MIC<sub>50</sub>: 0.5 µg/mL) also inhibited 98.0% of the isolates, and the rate of susceptibility to ciprofloxacin (MIC<sub>50</sub>: 0.5 µg/mL) was significantly lower. Trimethoprim-sulfamethoxazole showed reasonable activity. Among the β-lactams, the most active agents overall were piperacillin-tazobactam (MIC<sub>50</sub>: 4 µg/mL; 80.0% susceptibility), piperacillin (MIC<sub>50</sub>: 8 µg/mL; 74.0% susceptibility), and cefepime (MIC<sub>50</sub>: 8 µg/mL; 62.0% susceptibility). The carbapenems (6% to 12% susceptible) and the aminoglycosides (8% to 14% susceptible) exhibited poor activity against these pathogens.<sup>14</sup>

## Conclusion

*C. indologenes* should be considered as a potential pathogen in newborns in the presence of invasive equipment or on treatment with long-term broad-spectrum antibiotics. Appropriate choice of effective antimicrobial agents for treatment is difficult because of the unpredictability and breadth of antimicrobial resistance of these organisms, which often involves resistance to many of the antibiotics chosen empirically for serious Gram-negative infections.

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# Early Blood Glucose Profile and Neurodevelopmental Outcome at Two Years in Neonatal Hypoxic-Ischemic Encephalopathy

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## Abstract

**Background:** To examine the blood glucose profile and the relationship between blood glucose levels and neurodevelopmental outcome in term infants with hypoxic-ischaemic encephalopathy.

**Methods:** Blood glucose values within 72 hours of birth were collected from 52 term infants with hypoxic-ischemic encephalopathy. Hypoglycemia [ $< 46.8$  mg/dL (2.6 mmol/L)] and hyperglycemia [ $> 150$  mg/dL (8.3 mmol/L)] were correlated to neurodevelopmental outcome at 24 months of age.

**Results:** Four fifths of the 468 blood samples were in the normoglycemic range (392/468:83.8%). Of the remaining 76 samples, 51.3% were in the hypoglycemic range and (48.7%) were hyperglycemic. A quarter of the hypoglycemic samples (28.2%:11/39) and a third of the hyperglycemic samples (32.4%:12/37) were recorded within the first 30 minutes of life. Mean (SD) blood glucose values did not differ between infants with normal and abnormal outcomes [4.89(2.28) mmol/L and 5.02(2.35) mmol/L,  $p$  value = 0.15] respectively. In term infants with hypoxic-ischemic encephalopathy, early hypoglycemia (between 0-6 hours of life) was associated with adverse outcome at 24 months of age [OR = 5.8, CI = 1.04-32]. On multivariate analysis to adjust for grade of HIE this association was not statistically significant. Late hypoglycemia (6-72 hours of life) was not associated with abnormal outcome [OR = 0.22, CI (0.04-1.14)]. The occurrence of hyperglycemia was not associated with adverse outcome.

**Conclusion:** During the first 72 hours of life, blood glucose profile in infants with hypoxic-ischemic encephalopathy varies widely despite a management protocol. Early hypoglycemia (0-6 hours of life) was associated with severe HIE, and thereby; adverse outcome.

## Background

Hypoxic-ischemic encephalopathy (HIE) remains an important cause of neonatal death and long-term neurodisability.<sup>1</sup> Goals of management have been to maintain normoxemia, normocapnia,

normoglycemia and normal blood pressure to avoid or ameliorate secondary cerebral injuries.<sup>2</sup>

Neonatal hypoglycemia, independent of HIE, has been associated with adverse outcome in both term and preterm infants.<sup>3-5</sup> However, no conclusive evidence on the severity and duration of hypoglycemia causing brain damage has been reported.<sup>6,7</sup> Basu et al showed that the degree of hypoglycemia was correlated to the severity of HIE in term asphyxiated newborns.<sup>8</sup> In term infants with severe fetal acidemia, an association between early adverse outcome and hypoglycemia on the first blood sample was reported by Salhab et al.<sup>9</sup> These studies did not address long-term neurodevelopmental outcome. The mechanism of hypoglycemic brain injury has been examined in animal models. Hypoglycemia decreases the cerebrovascular response to hypoxia and increases cerebral superoxide production and aspartate levels into the brain extracellular space resulting in neuronal necrosis.<sup>10-12</sup>

Hyperglycemia is associated with adverse outcome in premature infants, in critically ill children and in adult patients with stroke.<sup>13-18</sup> In extremely low birth weight infants and in patients in pediatric intensive care unit, controlling elevated blood glucose levels by controlled insulin infusion was associated with good short-term outcome.<sup>19,20</sup> However, no data on long-term neurodevelopmental outcome relating to hyperglycemia in neonatal HIE has been reported.<sup>19,20</sup> The mechanism of hyperglycemic brain damage is thought to be related to neuronal cell apoptosis following reperfusion with high level of substrate (glucose) in an ATP- depleted cell. In an animal model, hyperglycemia following hypoxic-ischemic insult decreases fetal brain ATP and oxygen consumption and increases thickness of vascular endothelium with foci of infarction.<sup>21-23</sup>

In the absence of long-term neurodevelopmental outcomes on the effects of early hypoglycemia and hyperglycemia in HIE, the aim of this study was to describe the early blood glucose profile and to determine whether hypoglycemia and hyperglycemia in the 72 hours of birth were associated with adverse neurodevelopmental outcome at 24 months of age in infants with HIE.

## Methods

This study was a retrospective analysis of a prospective cohort of babies with HIE, none of whom received therapeutic hypothermia. It was conducted in a large maternity hospital with an annual delivery rate of approximately 5000 babies.

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**Table 1:** Demographic data

Total number of infants, n	52
Male, n (%)	34/52 (65.4%)
Infants required ETT at delivery, n (%)	32/52 (61.5%)
Infants required CPR at delivery, n (%)	13/52 (25%)
Birth Weight, median (range)	3.54(1.83-5.04)
Gestational age (weeks+days), median (range)	40+1(35+6-42+1)
Apgar at 1 minute, median (range)	4 (0-9)
Apgar at 5 minutes, median (range)	6 (2-10)
Blood glucose, median (range)	4.5 mmol/L [81 mg/dL], (0.3-17 mmol/L [5.4-306 mg/dL])
Abnormal outcome, n (%)	21/52 (40.4%), of those 2 infants had mild, 10 had moderate and 9 had severe HIE
Seizures	12/52 (23%)
Mortality	Mild HIE: 0/25 Moderate HIE: 2/18 (11%) Severe HIE: 2/9 (22%)

Apgar scores were not available in 4 infants with planned home deliveries; ETT= Endotracheal tube; CRP= Cardiopulmonary resuscitation.

Ethical approval was obtained from Cork University Hospital Research Ethics Committee. Informed consent was obtained from all parents of the infants who were enrolled in the study. We examined the medical notes of a cohort of 55 term infants with HIE, recruited prospectively at birth between May 2003 and December 2005. Term infants were recruited to the cohort if they fulfilled 2 or more of the following criteria: Initial capillary or arterial pH < 7.1; Apgar score < 5 at 5 minutes; Initial capillary or arterial lactate > 7 mmol/L; Abnormal neurology or clinical seizures.

Demographics and data related to neonatal course, ventilation variables and the arterial, capillary and venous blood glucose values of the first 3 days of life were retrieved from the medical notes. All infants with HIE had blood glucose levels checked within the first 30 minutes after delivery. Blood glucose values were collected from either arterial, venous, or capillary samples. An on-site analyser (Radiometer) was used to measure blood glucose levels. Hypoglycemia and hyperglycemia were defined as blood glucose levels < 46.8 mg/dL (2.6 mmol/L) and > 150 mg/dL (8.3 mmol) respectively<sup>5,13</sup>

Hypoglycemia was treated with an initial parenteral bolus of 2 mL/kg of a 10% dextrose solution over one minute. Blood glucose levels were rechecked 30 minutes to 1 hour later according to the severity of hypoglycemia. Dextrose infusion rate or concentration was adjusted to maintain blood glucose level > 50 mg/dL (2.8 mmol/L). In infants with hyperglycemia, the rate or concentration of glucose infusion was adjusted to maintain blood glucose within normal levels.

**Table 2:** Relationship between blood glucose levels and adverse outcome in term infants with HIE (n=52; however in 7 infants there were both hypoglycaemic and hyperglycaemic episodes documented, explaining the overlap)

	No. of infants (n=52)	No. of infants With abnormal outcome	Risk of adverse outcome OR (CI)
Normoglycaemia	24/52	9/24 (37.5%)	OR = 0.8, (CI= 0.26-2.44)
Early hypoglycaemia (0-6 hours of life)	8/52	6/8 (75%)	OR= 5.8, (CI= 1.04-32)
Late hypoglycaemia (6-72 hours of life)	12/52	2/12 (8.3%)	OR= 0.22, (CI= 0.04-1.14)
Early hyperglycaemia (0-6 hours of life)	11/52	4/11 (36.4%)	OR=0.81, (CI=0.2-3.2)
Late hyperglycaemia (6-72 hours of life)	4/52	2/4 (50%)	OR= 1.53, (CI=0.2-11.8)

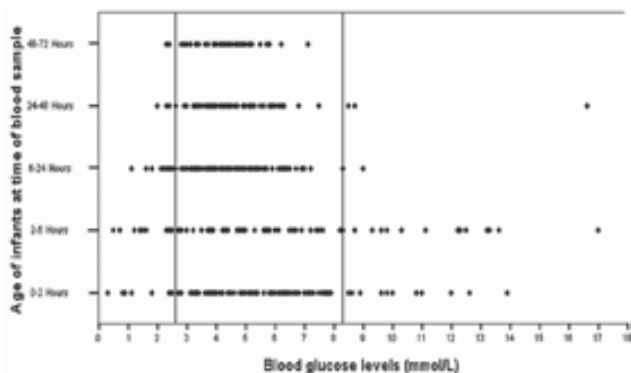
Demographic details and clinical data were recorded in each case. Clinical grade of encephalopathy was assigned using a Sarnat score at 24 hours of age. Neurodevelopmental outcome was assessed at 24 months using the Revised Griffith's scales of Mental Development.<sup>24</sup> Adverse outcome was defined as death, a Griffith's Quotient (GQ) less than 87, or significant motor disability. Statistical analysis was performed using SPSS version 14.0 for Windows. Summary measures were calculated and are reported as mean and standard deviation (SD) or median and (range). Spearman correlation was used to explore the differences in categorical variables. Univariate and multivariate logistic regression models were used to estimate odds ratios and 95% confidence intervals. A p value <0.05 was considered statistically significant.

## Results

Demographics (table 1): Fifty-two of the 55 infants completed follow up to 24 months. Mean (SD) gestational age was 39 weeks+1 day (1.5 weeks), mean (SD) birth weight was 3.45 (0.58) Kgs. Four infants were delivered at home, and therefore accurate details of Apgar scores and resuscitation details were not available. More than 1 bolus of dextrose infusion was required in four infants. All infants who required increased glucose infusions experienced stable blood glucose within 2 hours of birth.

72-hour glucose profile: In total, 468 blood glucose samples were analyzed. Four out of 5 samples were in the normoglycemic range (392/468: 83.8%). Of the remaining 76 samples, half (51.3%) were in the hypoglycemic range and less than half were hyperglycemic (48.7%). The median timing of initial blood glucose sampling was 25 and 80 minutes after birth (range 9-30 and 70-100 minutes) in inborn and outborn infants respectively. More than one third of all blood samples [177/468 (37.8%)] were documented within the first 6 hours of birth. A quarter of the hypoglycemic (28.2%: 11/39) and a third of the hyperglycemic samples (32.4%:12/37) were recorded on the first blood samples. Fifty percent (20/39) of the hypoglycemic and 90% (33/37) of the hyperglycemic samples were recorded within the first 6 hours of life (figure 1).





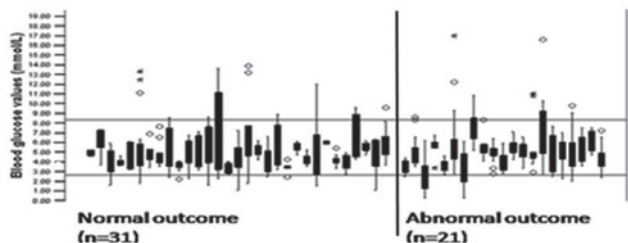
**Figure 1.** Distribution of blood glucose levels (mmol/L) according to the timing of blood glucose sample after delivery. Horizontal lines represent normal range of blood glucose.

Of the 52 infants in the cohort, mild, moderate and severe HIE was seen in 25, 18 and 9 infants, respectively. The mean (SD) number of blood glucose samples, taken in the first 72 hours, was 5.9 (2.9), 11.5 (5.7) and 13.1 (3.6) in infants with mild, moderate and severe HIE, respectively.

**Mean glucose levels and outcome:** Abnormal neurodevelopmental outcome at 24 months of age was documented in 21 (40.4%) infants. Mean (SD) blood glucose values did not differ between infants with normal or abnormal outcomes [4.89 (2.28) mmol/L and 5.02 (2.35) mmol/L,  $p$  value = 0.15] respectively. The distribution of blood glucose levels (mmol/L) in individual infants according to outcome is depicted in figure 2.

**HIE grade, glucose profile and outcome:** Mean (SD) of blood glucose level was 4.7 (1.8), 4.9 (2.4) and 5.3 (2.5) mmol/L in infants with mild, moderate and severe HIE respectively, ( $p$  value 0.10). The occurrence of early hypoglycemia correlated significantly with severe HIE ( $p$  = 0.012). Twenty-five infants had mild HIE, of whom 23/25 (92%) had a normal outcome. Moderate HIE occurred in 18 infants, of whom 10/18 (55.6%) had abnormal outcome. The nine infants with severe HIE all had an abnormal outcome.

**Infants with normoglycemia, hypoglycemia and hyperglycemia and outcome (table 2):** The relationship between early (0-6 hours of life) and late (6-72 hours of life) blood glucose levels and adverse outcome at 24 months of age in infants with HIE is presented in table 2. Early hypoglycemia (0-6 hours of life) was



**Figure 2.** Distribution of blood glucose levels (mmol/L) in individual infants ( $n=52$ ) by neurodevelopmental outcome at 24 months. Horizontal lines represent normal range of blood glucose. The boxes and whiskers represent the ranges between 25th and 75th percentiles and between 10th and 90th percentiles respectively. The circles (outliers) represent cases with values that are between 1.5 and 3 box lengths from either end of the box. Asterisks (extremes) represent cases with values more than 3 box lengths from either end of the box.

associated with adverse outcome (OR = 5.8, CI = 1.04-32). Late hypoglycemia (between 6-72 hours of life) and early and late hyperglycemia (0- 6 and 6-72 hours of life, respectively) were not associated with adverse outcome (table 2). Univariate followed by multivariate analysis had been performed. By univariate analysis, three variables were associated with adverse outcome: early hypoglycemia, Apgar score  $\leq 5$  at five minutes and severe HIE ( $p$  value 0.025, 0.035 and  $<0.001$  respectively). Moderate HIE, Apgar score at 1 minute, number of blood samples per subject and the requirement for intubation at birth were not significantly associated with adverse outcome. On multivariate analysis only moderate ( $p$  = 0.024) and severe ( $p$  < 0.001) HIE grade remained significantly associated with adverse outcome.

## Discussion

This study is the first to describe the blood glucose profile during the first 72 hours of life in infants with HIE. Despite a protocolized-driven approach to detecting and treating abnormal blood sugars following perinatal asphyxia in our unit, sustained normoglycemia in the first 72 hours of birth was observed in only half of our infants with HIE.

What does the glucose profile in HIE tell us? Abnormal blood glucose values were observed in 1 out of 6 samples. Less than a third of hypoglycemia and hyperglycemia episodes were observed on the first blood sample taken within a half-hour of birth. However, half of hypoglycemic samples and 90% of hyperglycemic samples occurred within 6 hours of birth. These findings suggest that many asphyxiated babies, in addition to facing an hypoxic-ischemic insult, are concurrently experiencing significant variations in blood sugars in the early newborn period. The hypoglycemic episodes may be due to perinatal depletion of glycogen stores (many asphyxiated babies are post mature), whilst the hyperglycemic episodes may reflect the release of stress-related hormones. In addition, since variations in blood glucose levels persist throughout the first 72 hours, this study indicates that regular measurements of the blood glucose should continue throughout this period.

In our study, early hypoglycemia was associated with an increased risk of adverse outcome at 24 months of age in infants with HIE. However, when corrected for grade of HIE this was no longer significant. Our results are consistent with the findings of Salhab et al. In that study, hypoglycemia on the initial blood sample after birth was associated with abnormal short-term outcomes (death as a consequence of severe encephalopathy and evidence of moderate to severe encephalopathy with or without seizures) in term infants with severe fetal acidaemia.<sup>9</sup> However no long term outcome has been reported from that group. In preterm infants, it has been shown that hypoglycemia was associated with mental and motor development scores at age of 18 months corrected. However at age of 8 years, only arithmetic and motor scores were affected.<sup>5,25</sup> It has been shown that intracranial MRI abnormalities in full term infants with neonatal hypoglycemia are resolved two months later.<sup>26</sup> Hypoglycemia has been associated with abnormal neurological outcomes but not with abnormal psychomotor development.<sup>3,27,28</sup>

Available data on the relationship between hyperglycemia and adverse outcome is inconclusive.<sup>13-15</sup> In infant rats, it has been shown that hyperglycemia during an hypoxic-ischaemic insult can have a beneficial effect against brain injury.<sup>29</sup> LeBlanc et al showed that, in newborn piglets, hyperglycemia after hypoxic-ischemic injury does not worsen the brain injury.<sup>30</sup> In newborn

piglets, Park et al showed that brain energy metabolism was affected by hyperglycemia during the immediate reperfusion period after hypoxic-ischemic brain insult.<sup>21</sup> In fetal sheep, Blomstrand S et al showed that hyperglycemia during asphyxia reduces cerebral oxygen consumption and increases acidosis.<sup>22</sup> Hyperglycemia following hypoxia-ischemia insult was shown to be harmful, in adult rats.<sup>23</sup>

However the glucose values studied were beyond those we see in clinical situation in humans. Despite the data on ELBW infants<sup>13-15</sup> and experience with older children,<sup>16,17</sup> the ideal management of hyperglycemia in neonatal encephalopathy remains unclear.<sup>19,20</sup>

There are some limitations to the current study. Data was available in only 52 patients who are part of an ongoing study of continuous early EEG in HIE. The association between blood glucose and neuro-developmental outcome was not an a priori outcome in this study. Standard blood sampling was not possible, since in emergency situations, blood glucose samples were collected from arterial, capillary or venous blood which may independently affect glucose levels. Initial blood glucose samples were collected within 30 and 100 minutes after delivery in inborn and outborn infants respectively. These were repeated between 30 minutes and 4 hours, as clinically indicated. It is, therefore, possible that there were variations in blood glucose values that were missed in between measurements. Finally this cohort of neonates with HIE was recruited prior to introduction of therapeutic hypothermia as a standard of care. Whether variations in blood glucose will affect neuro-developmental outcome in infants treated with therapeutic hypothermia remains to be seen.

## Conclusion

We conclude that it is difficult to avoid hypoglycemia and/or hyperglycemia in infants with HIE, since such variations in blood glucose levels often occur soon after birth, and may be related to the asphyxial process. In term infants with HIE, glucose profiles vary widely during the first 72 hours of life. Early hypoglycemia occurs more frequently in infants with severe HIE, and is therefore associated with abnormal outcome. The further exploration of the relationship between glycemic control and neurological outcome will require larger numbers of patients and continuous blood glucose monitoring.

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# Reverse End-Diastolic Flow in a Fetus with a Rare Liver Malformation

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## Abstract

**Introduction:** We describe a case of early and persistent reverse end-diastolic flow in the middle cerebral artery in a fetus with severe ascites. These features are associated with a rare liver malformation known as ductal plate malformation.

**Case presentation:** A 28-year-old Caucasian woman was referred to our high-risk obstetric unit at 24 weeks' gestation for fetal ascites detected during a routine ultrasound examination. During her hospitalization we performed medical investigations, including a fetal paracentesis, to detect the etiology of fetal ascites. The cause of fetal ascites (then considered non-immune or idiopathic) was not evident, but a subsequent ultrasound examination at 27 weeks' gestation showed a reverse end-diastolic flow in the middle cerebral artery without any other Doppler abnormalities. A cesarean section was performed at 28 weeks' gestation because of the compromised fetal condition. An autopsy revealed a rare malformation of intrahepatic bile ducts known as ductal plate malformation.

**Conclusion:** Persistent reverse flow in the middle cerebral artery should be considered a marker of adverse pregnancy outcome. We recommend careful ultrasound monitoring in the presence of this ultrasonographic sign to exclude any other cause of increased intracranial pressure. To better understand the nature of these ultrasonographic signs, additional reports are deemed necessary. In fact in our case, as confirmed by histopathological examination, the fetal condition was extremely compromised due to failure of the fetal liver. Ductal plate malformation altered the liver structures causing hypoproteinemia and probably portal hypertension. These two conditions therefore explain the severe hydrops that compromised the fetal situation.

## Introduction

Our study analyzes a case of reverse end-diastolic flow in the middle cerebral artery (MCA) in a fetus at 26 weeks' gestation with a previous diagnosis of idiopathic ascites. This particular ultrasound pattern was associated with a rare liver abnormality known as ductal plate malformation (DPM). This condition is a rare malformation of intrahepatic bile ducts (IHBDs) due to an arrest or failure of epitheliomesenchymal inductive interactions.

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Immature bile ducts are subject to a progressive destructive cholangiopathy, resulting in a pattern of a more or less advanced fetal type of liver fibrosis.<sup>1</sup> The disequilibrium of the portobiliary system is often associated with autosomal recessive polycystic kidney disease or other fibrocystic malformation of the liver or kidneys, even if it has also been reported as an isolated entity<sup>2</sup> that is usually not identified by prenatal ultrasound examination. Only in rare cases of prenatal onset fetal liver cysts can be seen, and an ultrasound scan is the most useful method in showing the kidneys' anomalies associated with renal disease.<sup>3</sup> Reverse flow in the MCA is usually a transient event. The occurrence of this particular waveform can be explained by a few possible mechanisms that could alter cerebral blood circulation. Reverse flow could be a consequence of any elevated pressure condition outside or inside the brain. An elevation of external pressure can be due to mechanical compression of the fetal head by the transducer, which may induce a reverse flow that causes a high impedance to blood flow in the cerebral circulation.<sup>4</sup> External pressure may be increased also in the presence of an extended oligohydramnios or anhydramnios.<sup>5</sup> An increase in internal pressure can be due to the occurrence of hydrocephalus, cerebral edema, or cerebral hemorrhage. All of these pathological events can explain reverse flow in the MCA.<sup>6,7</sup> Reverse flow could also represent the extreme form of a brain-sparing mechanism before fetal death in case of intra-uterine growth restriction (IUGR).<sup>8</sup> The other elements that can explain the reversal of flow in the MCA include abnormal fetal heart rate, the presence of tricuspid regurgitation, maternal drug effect, and temporary changes in fetal blood pressure after invasive intra-uterine procedures.<sup>9</sup>

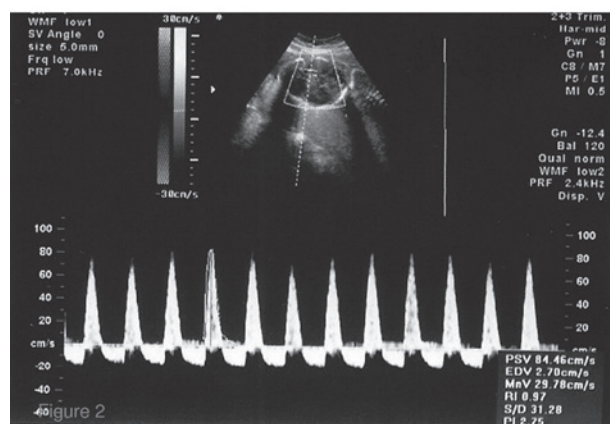
## Case Presentation

A 28-year-old Caucasian woman, gravida 4, para 1, was referred to our high-risk obstetric unit at 24 weeks' gestation for fetal ascites detected during a routine ultrasound examination. Her personal and family history did not reveal any pathology of note. Her first pregnancy ended with an intra-uterine death at 23 weeks' gestation caused by chorioamnionitis. In the second pregnancy, a live baby girl was delivered at 40 weeks' gestation. Four years later our patient had a spontaneous miscarriage. Our patient denied any fever, rash, cold symptoms, or joint pain before and during pregnancy. She did not refer to any vaginal bleeding. Laboratory tests for Toxoplasma and rubeola showed negative immunoglobulin M (IgM). An ultrasound examination performed during the consultation confirmed the presence of abdominal ascites (Figure 1). A borderline monolateral dilation of the cerebral ventricle was also seen.



**Figure 1.** Sonogram showing fetal ascites.

Biometry of the fetal limbs was below the mean in relation to gestational age, while cephalic measurements were normal. No other fetal anomalies were observed. Amniotic fluid was present in adequate quantity, but fetal movements were poor. For these reasons, the woman was admitted to our institution for close pregnancy monitoring. During hospitalization, her blood pressure and heart frequency were measured several times during the day, while cardiotocography was performed twice a day. Maternal blood pressure was normal, and there was no proteinuria. Investigation about the etiology of the fetal ascites were carried out, and a fetal paracentesis was also performed. Both parents had normal mean corpuscular erythrocyte volume with no sign of microcythemia and they both had positive blood group Rh without any pathologic antibodies. A routine blood laboratory assessment did not show any kind of abnormalities. Viral serology markers (cytomegalovirus IgG and IgM, parvovirus IgG and IgM) were negative in the maternal blood, and no viral genome was isolated in her amniotic fluid or the fetal ascites sample. The fetal karyotype was normal (46, XY). A Kleihauer-Betke test showed no evidence of fetal erythrocytes in the maternal circulation. Immunologic markers, lupus anticoagulant anticardiolipin, antinuclear, and anti-RO antibodies were negative; G6PD was also excluded. There was no evidence regarding the cause of fetal ascites (then considered non-immune or idiopathic). Only a mild increase in inflammation indices was noted (VES 40, PCR 7.325); an antibiotic preventive treatment was performed for five days (sulbactam/ampicillin 1.5 mg three times daily, gentamicin 80 mg three times daily, metronidazole 500 mg three times daily). During hospitalization, detailed ultrasound scans were performed at least every two days to monitor the ascites and general condition of the fetus. Fetal middle cerebral artery peak systolic velocity (PSV) was measured to diagnose fetal anemia. Pulsatility index (PI) of either the umbilical artery (UA) or the MCA as well as the resistance index of uterine arteries were assessed to better evaluate the materno-fetal perfusion. Monitoring scans showed a deterioration of fetal condition. Paracentesis was performed at 25 weeks' gestation, but two days later the fetal ascites occurred again. A restriction of fetal growth and progressive reduction of amniotic fluid were also registered. The value of PSV in the MCA was borderline for moderate to severe anemia according to Mari's chart,<sup>10</sup> whereas fetal Doppler ultrasound parameters were normal. At 27 weeks' gestation, a reverse end-diastolic flow in the MCA occurred (Figure 2). This abnormal waveform pattern persisted for all the ultrasound examinations, and it was not associated with other Doppler abnormalities (PI UA 1.15, PI MCA 1.54). The condition was interpreted as 'at risk', and our patient



**Figure 2.** Sonogram showing reverse flow in the MCA.

was submitted to closer monitoring. Fetal echocardiography showed cardiomegaly without significant abnormality of heart structures and a mild tricuspid regurgitation. Cardiotocography monitoring showed fetal bradycardia (fetal heart rate 100 beats per minute). Our patient was submitted to fetal magnetic resonance imaging to investigate in particular the brain edema, and this confirmed the presence of fetal ascites without showing any abnormality of fetal cerebral tissue or signs of hypoxia. Corticosteroid treatment (betamethasone 12 mg for two days) was started because of a high risk for preterm delivery. After one week, ultrasound parameters showed a severe decrease in fetal weight (<fifth percentile), an increase in fetal ascites, and subcutaneous edema. The reversed end-diastolic flow in the MCA persisted, and an increase of PI UA was detected. Alterations of ductus venosus waveform appeared, and an inversion of "a" wave was identified. The amniotic fluid index was below the mean for gestational age. The biophysical profile examination was unsatisfactory. The severe prognosis was explained to the couple, and an active intervention was ruled out. The fetus was in breech presentation at this time. Our patient was submitted to an emergency cesarean section at 28 weeks' gestation. A live baby boy in poor general condition was delivered. The Apgar score was one and five. Intubation was necessary, but despite neonatal intensive care, the baby died a few hours after birth. An autopsy revealed a rare malformation of IHBs known as DPM. No other anomaly was identified.

## Discussion

Currently, Doppler ultrasound is widely used to study fetal circulation in both normal and pathological pregnancy. With regard to fetal cerebral circulation, quantitative and qualitative estimations of the MCA blood flow are usually performed. Blood flow impedance is studied in terms of PI in relation to gestational age; the qualitative assessment consists of a valuation of present, absent, or reverse blood flow during the diastole. Reverse end-diastolic flow in the MCA is usually a rare and transient event. In the majority of cases, the cause of this abnormal waveform pattern remains unknown even when increased cerebral pressure is considered. Sepulveda et al.<sup>11</sup> considered reverse flow in the MCA an agonal sign in the human fetus. They documented the first case in the literature of reverse end-diastolic flow in a severely growth-restricted fetus that appeared the day before fetal death. Leung et al.<sup>12</sup> documented this pattern waveform as a transient event in a severe IUGR fetus at 24 weeks' gestation. During the observation, the fetus was in breech presentation. Reverse flow in the MCA disappeared the day after, when the fetus modified its presentation in a cephalic one and did not

come out again in the subsequent Doppler studies. These authors underlined that the fetus was in breech presentation when the reverse flow occurred in the MCA, whereas it was in cephalic presentation before and after. De Spirlet et al.<sup>13</sup> described a case of persistent reverse end-diastolic flow in a fetus with subdural hematoma due to severe thrombocytopenia. Respondek et al.<sup>9</sup> analyzed the outcome of 22 fetuses with reversal of diastolic flow in the MCA. The authors concluded that, in the majority of cases, this phenomenon is not related to fetal pathology, morbidity, and mortality. In their case, an intra-uterine death was observed in a fetus with a prolonged reverse flow in the MCA. In our case, we carefully minimized the transducer's pressure when the reversal of diastolic flow in the MCA appeared. We also used two different types of ultrasound equipment and either a trans-vaginal or trans-abdominal approach. No uterine contractions were observed during the examination. Despite all of these efforts, the waveform patterns persisted for the duration of ultrasound examination. The fetus also presented with bradycardia (<100 beats per minute) and a mild tricuspid regurgitation assessed during the echocardiography. This regurgitation was defined as not significant for the hemodynamic status of the fetal heart, and we assume that this was not correlated to the reversal of diastolic flow in the MCA. The peculiarity in this case was that in our patient, reverse flow in the MCA persisted for over one week and was not associated with reverse flow in the UA. However, it could be related to a deterioration of fetal condition.

## Conclusions

We agree with Sepulveda et al.<sup>11</sup> in considering reverse end-diastolic flow in the MCA a sign of poor fetal outcome. In fact, as confirmed by histopathological examination, the fetal condition in our case was extremely compromised by failure of the fetal liver. The DPM altered the liver structures, causing hypoproteinemia and probably portal hypertension. These two conditions can explain the severe hydrops that compromised the fetal condition. According to the literature, no ultrasound sign of liver disease can be seen on prenatal ultrasound examination.<sup>3</sup> To the best of our knowledge, there is only one case in the literature of fetal ascites associated with DPM.<sup>14</sup> In that case, the massive ascites appeared later in gestation (33 weeks), and the baby died at 36 days of life despite intensive neonatal care. Regarding our experience, isolated and persistent reverse flow in the MCA should be considered a marker of adverse pregnancy outcome. In this condition, we recommend close ultrasound monitoring to exclude any cause of increased intracranial pressure and to identify other signs of impending fetal adverse outcome. We recommend repeated ultrasound and Doppler assessments at not more than daily intervals. To better understand the nature of this ultrasound sign and its relation with poor fetal outcome, additional reports are deemed necessary.

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# Evidence-Based Medicine Training During Residency

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## Abstract

**Background:** Evidence-based medicine (EBM) has been widely integrated into residency curricula, although results of randomized controlled trials and long term outcomes of EBM educational interventions are lacking. We sought to determine if an EBM workshop improved internal medicine residents' EBM knowledge and skills and use of secondary evidence resources.

**Methods:** This randomized controlled trial included 48 internal medicine residents at an academic medical center. Twenty-three residents were randomized to attend a 4-hour interactive workshop in their PGY-2 year. All residents completed a 25-item EBM knowledge and skills test and a self-reported survey of literature searching and resource usage in their PGY-1, PGY-2, and PGY-3 years.

**Results:** There was no difference in mean EBM test scores between the workshop and control groups at PGY-2 or PGY-3. However, mean EBM test scores significantly increased over time for both groups in PGY-2 and PGY-3. Literature searches, and resource usage also increased significantly in both groups after the PGY-1 year.

**Conclusions:** We were unable to detect a difference in EBM knowledge between residents who did and did not participate in our workshop. Significant improvement over time in EBM scores, however, suggests EBM skills were learned during residency. Future rigorous studies should determine the best methods for improving residents' EBM skills as well as their ability to apply evidence during clinical practice.

## Background

Competent clinical decision-making is a complex and critical process<sup>1</sup> and leaders in graduate medical education have long sought to hone residents' decision-making skills.<sup>2</sup> The introduction of evidence-based medicine (EBM) in 1992<sup>3</sup> and its subsequent inclusion by the Accreditation Council for Graduate Medical Education (ACGME) as a core component of practice-based learning and improvement<sup>4</sup> served as a catalyst for residency programs to incorporate evidence-based practice concepts into their curricula.<sup>5</sup>

After two decades and a multitude of systematic reviews, non-randomized controlled studies, and pre- and post-intervention studies, the impact of formal EBM training on resident knowledge, skills, attitudes, and behavior remains unclear.<sup>6</sup> Challenges remain for translating EBM knowledge into clinical practice,<sup>7,8</sup> and barriers to successful implementation of EBM skills have not yet been resolved.<sup>9</sup> Determination of the best methods for teaching clinical decision-making has been made difficult by the lack of well-validated evaluation tools and the absence of randomized controlled trials evaluating the impact of EBM educational interventions.<sup>10,11</sup> This paper reports results from a long-term, randomized controlled trial designed to test the hypothesis that participation in a brief interactive EBM workshop leads to increases in residents' EBM knowledge, literature searching, and self-reported use of evidence-based resources. Improvements in EBM competency are assessed across residency training in an effort to elucidate how best to prepare residents for effective clinical decision-making.

## Methods

In May 2003 and May 2004, all categorical PGY-1 (postgraduate year 1) residents from two successive classes in the University of Wisconsin-Madison Internal Medicine Residency program completed an EBM knowledge and skills pre-test (Figure 1). Approximately half of the residents in each class were then randomized by computer-generated random numbers either to a treatment group (12 in 2003, 11 in 2004) where they participated in an EBM workshop during the fall of their PGY-2 year, or to a control group where they did not attend the workshop (14 in 2003, 11 in 2004). Six and 18 months later, in May of their PGY-2 and PGY-3 years, residents again completed EBM knowledge tests. This study protocol was approved by the University of Wisconsin Health Sciences Institutional Review Board. All residents received Institutional Review Board approved study information sheets prior to participation and provided implied consent by completing the EBM tests and surveys.

Residents in the treatment group participated in an interactive 4-hour EBM workshop, co-conducted by one faculty member (DF) and one librarian. The workshop, which took place in a computer lab, emphasized four steps in the EBM process: a) developing an answerable question, b) finding the best available evidence, c) evaluating the evidence, and d) applying the evidence to a patient care decision. The case-based teaching covered both therapeutic and diagnostic patient care decisions. Individual and group exercises focused on developing and refining clinical questions in the PICO (Patient, Intervention,

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Comparison, Outcome) format;<sup>12</sup> individually searching multiple evidence databases; evaluating individual articles for validity; calculating absolute risk reductions (ARR), numbers needed to treat (NNT), relative risk reductions (RRR) and likelihood ratios; and applying evidence to a patient care decision.

The only other formal EBM training that residents received during the study period was an EBM journal club. Each resident presented at journal club once during their PGY-3 year. They met with an advisor to develop a clinical question, and to search for and critically appraise the appropriate evidence. They presented the case and findings to other residents and internal medicine faculty during journal club.

Residents were given 40 minutes to complete an EBM test of knowledge and skills that consisted of 25 multiple choice questions covering seven EBM focus areas: a) asking clinical questions, b) searching, c) EBM resources, d) critical appraisal of therapeutic and diagnostic evidence, e) calculating ARR, NNT, and RRR, f) interpreting diagnostic test results, and g) interpreting confidence intervals. The test items required application of EBM concepts. Each item was scored as either correct (1 point) or incorrect (0 points) for a maximum possible score of 25. The same test was used each year; all copies were collected immediately after completion and no feedback was provided to residents.

Our EBM test was developed by the first author (DF) in collaboration with a local EBM expert for a prior project with internal medicine residents.<sup>13</sup> It was revised based on item analysis to include five fewer questions and minor question rewording. Post-hoc construct validity was demonstrated by a one-way analysis of variance comparing the total EBM test scores of 10 first year medical students who had no previous exposure to EBM (M = 10.9, SD = 2.8) with the total EBM test scores of the 48 PGY-1 residents who participated in this study (M = 14.5, SD = 3.6) and 9 EBM experts (M = 22.9, SD = 2.1) who had served as teachers either in a national week-long EBM workshop or in a local EBM faculty development program. EBM experts earned significantly higher EBM test scores than PGY-1 residents ( $p < 0.001$ ), who in turn, earned significantly higher scores than first year medical students ( $p = 0.004$ ).

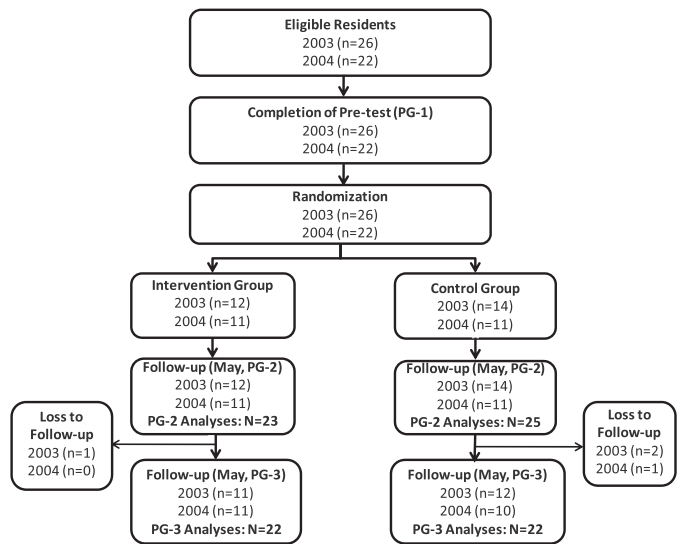


Figure 1 Study design and flow of study participants.

Responsiveness of the test was also demonstrated with 16 practicing clinicians during a faculty development fellowship that included EBM training. Mean difference in fellows' pre-test to post-test EBM scores was 5.8 points (95% CI, 4.2, 7.4).<sup>14</sup>

In May of each year, at the time of EBM test administration, residents were asked to complete a brief questionnaire self-reporting the number of literature searches they performed during the past week and the number of times they used each of five evidence-based resources in the past month (irrespective of which service they were on): UpToDate, MEDLINE, ACP Journal Club, Cochrane Database of Systematic Reviews (CDSR), and Database of Abstracts of Reviews of Effects (DARE). These resources were freely available to residents at the time the study was initiated. The number of self-reported literature searches was categorized as 0, 1-2, 3-5, 6-10, or more than 10 times per week. The use of evidence-based resources was categorized as 0, 1-2, 3-5, 6-10, or more than 10 times per month.

Residents who participated in the EBM workshop completed an anonymous 10-item self-assessment of their understanding and ability to practice EBM for therapeutic and diagnostic decision-making. They also responded to a single item evaluating the overall quality of the EBM workshop, rated on a 5-point Likert scale from strongly disagree (1) to strongly agree (5).

Data analysis: Analysis of covariance (ANCOVA) was used to test the effect of treatment group on residents' EBM test scores in the PGY-2 and PGY-3 years, while controlling for baseline (PGY-1) EBM test scores as a covariate. T-tests were conducted to test for group differences in the change of mean test scores between time points. T-tests and Cohen's d were calculated to estimate the changes and effect sizes of EBM test scores for all residents over residency years. The median number of self-reported searches and resources used were computed for each group, and Mann-Whitney U tests were used to assess for differences between groups at each time point, as well as to test for differences between residency years. Descriptive analyses convey residents' self-assessments of knowledge gained following the EBM workshop. Data were analyzed using SPSS for Windows version 16.

Table 1 Baseline characteristics of PGY-1 residents

Characteristic	Workshop (n = 23)	Control (n = 25)
Mean (SD)		
PGY-1 EBM Pre-Test Scores	13.7 (3.9)	15.3 (3.2)
No. of residents (%)		
Number of Searches (times per week)		
0	7 (30%)	3 (12%)
1 - 2	8 (35%)	11 (46%)
3 - 5	6 (26%)	6 (25%)
6 - 10	2 (9%)	4 (17%)
Resource Usage (in past month)		
UpToDate	23 (100%)	25 (100%)
MEDLINE	18 (78%)	18 (72%)
ACP Journal Club	4 (17%)	9 (36%)
CDSR	3 (13%)	5 (20%)
DARE	0 (0%)	1 (4%)

There were no significant differences ( $p < 0.05$ ) in baseline characteristics between workshop and control groups.

**Table 2 EBM test scores by postgraduate level**

	PGY-1			PGY-2				PGY-3			
	Mean	SD	n	Mean	SD	n	Change over PGY-1	Mean	SD	n	Change over PGY-1*
Workshop	13.65	3.88	23	15.52	3.95	23	1.87	17.09	3.89	22	3.00
Control	15.28	3.22	25	16.16	3.20	25	0.88	18.00	3.87	22	2.59
Combined Groups	14.50	3.61	48	15.85	3.55	48	1.35	17.55	3.86	44	2.80

\*Calculated among residents participating at both time points; does not equal the difference of the means presented in the table due to participant attrition.

## Results

All 48 residents completed EBM pre-tests and questionnaires during their PGY-1 year and EBM post-tests and questionnaires during their PGY-2 year. Forty-four (92%) residents also completed EBM post-tests and questionnaires during their PGY-3 year. Baseline characteristics including PGY-1 EBM pre-test scores for all residents, number of searches, and resource usage are presented in Table 1. There were no statistically significant differences between the workshop and control groups at baseline.

There were no significant differences in mean test scores between treatment groups at either time point following the EBM workshop; the workshop group scored slightly—but not significantly—lower at both time points. Similarly, there were no significant differences in the amount each group improved over their baseline scores at each time point, as shown in Table 2. The difference in the change in mean test scores from PGY-1 to PGY-2 between the workshop group (mean score increase of 1.87) and control group (mean score increase of 0.88) was 0.99 (95% CI: -0.62, 2.60, t-test p-value = 0.221). For the PGY-

1 to PGY-3 interval, the difference in the change in mean test scores was 0.41 (95% CI: -1.48, 2.29, t-test p-value = 0.664). After using ANCOVA models to adjust for baseline (PGY-1) scores, the differences between the workshop and control groups remained small at both time points. The adjusted mean score for the workshop group was 0.51 points higher (95% CI: -1.04, 2.05) than for the control group in the PGY-2 year ( $p = 0.510$ ), and 0.07 points higher (95% CI: -1.80, 1.93) in the PGY-3 year ( $p = 0.944$ ). Baseline test scores accounted for nearly all of the variance explained by the ANCOVA models ( $R^2 = 0.49$  for PGY-2) and ( $R^2 = 0.42$  for PGY-3), where low baseline scores were predictive of greater score increases at PGY-2 and PGY-3.

There was an overall increase in residents' mean EBM test scores over time. The mean score at PGY-2 was 1.35 points (95% CI: 0.55, 2.16) higher than at PGY-1 ( $p = 0.001$ ), Cohen's  $d = 0.49$ . The mean score at PGY-3 was 2.79 points (95% CI: 1.86, 3.73) higher than at PGY-1 ( $p < 0.001$ ), Cohen's  $d = 0.91$ .

Mann-Whitney U tests comparing residents in the treatment and control groups indicated similar numbers of literature searches

**Table 3 Literature searches and EBM resource usage per week, by treatment group and postgraduate level**

	PGY-1 (n = 48)		PGY-2 (n = 48**)		PGY-3 (n = 44)	
	Group	Median	p-value*	Group	Median	p-value*
<b>Total Literature Searches</b>						
Workshop		1.5	0.25		4.0	0.50
Control		1.5			4.0	0.48
<b>EBM Resource Usage</b>						
<b>Up To Date Searches</b>						
Workshop		10.0	0.46	> 10.0	> 10.0	0.37
Control		> 10.0		> 10.0	> 10.0	
<b>MEDLINE Searches</b>						
Workshop		1.5	0.65	8.0	6.0	0.68
Control		4.0		8.0	6.0	
<b>ACP Journal Club</b>						
Workshop		0.0	0.22	0.0	1.5	0.12
Control		0.0		0.0	1.5	
<b>CDSR</b>						
Workshop		0.0	0.66	1.5	1.5	0.74
Control		0.0		0.0	1.5	
<b>DARE</b>						
Workshop		0.0	0.34	0.0	0.0	0.71
Control		0.0		0.0	0.0	

\*Mann-Whitney U p-value calculated

\*\* Missing data for 1 resident on PGY-2 literature search item



during each of their three years of residency ( $p > 0.05$ ) (see Table 3). In terms of EBM resource usage, PGY-2 residents in the treatment group reported more frequent usage of CDSR than residents in the control group (median monthly uses of 1-2 and 0, respectively, Mann-Whitney U  $p = 0.025$ ), and slightly, but not significantly, higher usage of DARE (Mann-Whitney U  $p = 0.067$ ). No differences were found in the frequencies of other resources used in the PGY-2 year; and treatment and control groups did not differ on any of the resources used during the PGY-3 year ( $p > 0.05$ ).

PGY-3 residents reported a significantly greater number of literature searches than did PGY-1 residents: Median increase from 1-2 to 3-5 times per month (Mann-Whitney U  $p < 0.001$ ). PGY-3 residents also exhibited significantly greater utilization of all EBM resources than they had as PGY-1 residents: Median MEDLINE access increased from 3-5 to 6-10 uses per month ( $p = 0.038$ ); ACP Journal Club access increased from 0 to 1-2 uses per month ( $p < 0.001$ ); DARE usage increased significantly ( $p < 0.001$ ), although the median usage was less than once per month at both PGY-1 and PGY-3 levels; and UpToDate usage increased significantly ( $p = 0.038$ ), although residents generally reported using UpToDate  $>10$  times per month at both time points.

Residents' self-assessments of knowledge gained following the EBM workshop were consistently positive with average scores of 4.4 or above (on a 5-point Likert scale) in each of the following workshop content areas: Residents reported a better understanding of how to ask clinical questions about therapy ( $M = 4.5$ ,  $SD = 0.5$ ) and diagnosis ( $M = 4.4$ ,  $SD = 0.7$ ), how to search available databases for evidence about therapy ( $M = 4.9$ ,  $SD = 0.4$ ) and diagnoses ( $M = 4.8$ ,  $SD = 0.4$ ), and how to appraise the validity of therapeutic trials ( $M = 4.4$ ,  $SD = 0.5$ ) and interpret results of studies of diagnostic tests ( $M = 4.4$ ,  $SD = 0.5$ ). Residents consistently rated the workshop very highly ( $M = 4.5$ ,  $SD = 0.5$ ) and felt that participation in the workshop improved their ability to practice EBM ( $M = 4.5$ ,  $SD = 0.5$ ).

## Discussion

This randomized controlled trial assessed the impact of an EBM workshop on residents' EBM knowledge and skills within the context of residency training. Unlike previous short-term randomized<sup>15</sup> and non-randomized trials,<sup>12,16,17</sup> the results failed to indicate an independent effect of our 4-hr interactive EBM workshop on residents' EBM test performance. Although residents rated the EBM workshop very positively and reported perceived gains in EBM knowledge, their perceptions were not associated with increases in EBM skills.

Several limitations could have prevented us from documenting an effect of our EBM workshop on residents' EBM test scores. First, although the difference in change in PGY-1 to PGY-3 test scores between the treatment and control groups was small (0.41), the confidence intervals around this change included a possible medium effect size, and the small sample size may have limited our ability to detect differences that might be considered clinically or educationally significant. Second, knowledge is a dynamic construct that changes over time.<sup>18-20</sup> Our assessments were conducted 6 and 18 months following the intervention, so short-term increases in EBM knowledge could have been missed, or masked by shared learning if workshop participants effectively translated their EBM knowledge to non-workshop participants through journal club, critical reading projects, and

close interaction during clinical care. Third, although we did not assess residents' prior EBM training in medical school, we noted that our residents' baseline EBM test scores (58%) were actually much closer to the post-test scores reported by Smith et al.<sup>21</sup> (58-64%) and Fritsche et al.<sup>16</sup> (65%) than they were to the baseline scores reported in those studies (~40%). Although different tests were used in each study, it is possible that our residents' initially higher levels of EBM competency may have reduced their opportunities to demonstrate improvement.

Our results did, however, indicate significant improvement in residents' EBM knowledge, numbers of literature searches, and use of secondary evidence resources over the course of residency training. In addition, PGY-2 residents who participated in the workshop exhibited an increased use of CDSR and DARE compared with the control group. This is consistent with other randomized controlled trials demonstrating an increase in residents' use of evidence-based resources following EBM training<sup>15</sup> particularly when training focused on using secondary evidence resources instead of MEDLINE.

This study is one of only a few randomized controlled trials evaluating the impact of an EBM curriculum over the course of residency training. The fact that our results are inconsistent with some previous randomized controlled trials, for example, Kim et al. (2008), highlights the need for more rigorous, long-term trials of EBM education to provide guidance for implementing effective EBM programs. More intense doses of EBM education may be required to produce measurable improvement in residents' EBM skills.<sup>22</sup>

Research also suggests that integration of EBM training into clinical practice may provide better results in improving EBM skills,<sup>10</sup> although this has not been confirmed in randomized controlled trials. Furthermore, the true goal of EBM education is to improve resident behavior and patient outcomes. This will require a combination of educational interventions to teach basic skills, real time evidence access and incorporation of evidence into clinical care. Our data were collected from 2003-2006 and the change in the quality and availability of secondary resources since that time may require different methods of teaching and integration of EBM practices into clinical care.

Based on these results, our residency program has built a broader-based EBM curriculum that enhances faculty competencies, stimulates resident scholarship, and guides residents in their application of EBM at the point of care. We now provide separate interactive workshops for our PGY-1 and PGY-2 residents to allow time for reinforcement and consolidation of EBM skills. We are also integrating our EBM training into clinical care through piloting a new evidence-based "educational prescription" tool designed to walk residents through the steps of EBM while answering clinical questions at the point of care.<sup>23</sup> Validation of our evidence-based prescription tool as part of a multi-institutional trial will allow us to assess the generalizability of different types of EBM educational interventions and avoid issues of contamination that are common in single center studies.<sup>24</sup>

## Conclusions

This randomized controlled trial was not able to detect a significant effect of a 4-hour EBM workshop on residents' EBM knowledge and skills, although residents did demonstrate an increase in EBM skills, literature searching, and resource usage

over the course of residency training. Future multi-institutional randomized controlled studies are warranted to determine the best methods for improving residents' EBM skills as well as for enhancing their abilities to apply evidence during clinical practice.

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# Assessment of Surfactant Use in Preterm Infants as a Marker of NICU Quality

Heather C. Kaplan, Scott A. Lorch, Jennifer Pinto-Martin, Mary Putt, and Jeffrey H. Silber

## Abstract

**Background:** Proposed neonatal quality measures have included structural measures such as average daily census, and outcome measures such as mortality and rates of complications of prematurity. However, process measures have remained largely unexamined. The objective of this research was to examine variation in surfactant use as a possible process measure of neonatal quality.

**Methods:** We obtained data on infants 30 to 34 weeks gestation admitted with respiratory distress syndrome (RDS) within 48 hours of birth to 16 hospitals participating in the Pediatric Health Information Systems database from 2001-2006. Models were developed to describe hospital variation in surfactant use and identify patient and hospital predictors of use. Another cohort of all infants admitted within 24 hours of birth was used to obtain adjusted neonatal intensive care unit (NICU) mortality rates. To assess the construct validity of surfactant use as a quality metric, adjusted hospital rates of mortality and surfactant use were compared using Kendall's tau.

**Results:** Of 3,633 infants, 46% received surfactant. For individual hospitals, the adjusted odds of surfactant use varied from 2.2 times greater to 5.9 times less than the hospital with the median adjusted odds of surfactant use. Increased annual admissions of extremely low birth weight infants to the NICU were associated with greater surfactant use (OR 1.80, 95% CI 1.02-3.19). The correlation between adjusted hospital rates of surfactant use and in-hospital mortality was 0.37 (Kendall's tau  $p = 0.051$ ).

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**Conclusions:** Though results were encouraging, efforts to examine surfactant use in infants with RDS as a process measure reflecting quality of care revealed significant challenges. Difficulties related to adequate measurement including defining RDS using administrative data, accounting for care received prior to transfer, and adjusting for severity of illness will need to be addressed to improve the utility of this measure.

## Background

Measuring the quality of health care has become a major focus of policymakers, health care purchasers, and physicians. Traditionally, quality of care is measured by one of three dimensions—structure (characteristics of the environment in which care is delivered), process (care itself or what is actually done to a patient), or outcome (the patient's health status). Neonatal quality measures that have been examined include structural measures such as average daily census, and outcome measures such as mortality and rates of complications of prematurity. However, process measures of neonatal quality have remained largely unexamined.

The best processes to use as quality indicators are those linked to improved outcomes through sound scientific evidence.<sup>1,2</sup> Surfactant therapy for neonatal respiratory distress syndrome (RDS) serves as an excellent evidence-based process measure. In both very low birth weight (VLBW, <1500 grams)<sup>3</sup> and larger<sup>4-6</sup> preterm infants, it has been shown to lead to a significant decrease in the risk of mortality and pneumothorax.<sup>7,8</sup> Additionally, position statements from professional organizations support use of this proven therapy in infants of any gestational age with RDS.<sup>9-11</sup> However, while there is documented variation in the evidence-based use of surfactant among VLBW infants,<sup>12,13</sup> variation in evidence-based surfactant use among larger preterm infants—the most prevalent group of preterm infants—has not been examined. Additionally, given that a majority of preterm infants are delivered moderately preterm and these patients are not targeted by current quality measures, concerted efforts are needed to identify and validate measures targeting this patient population.<sup>14</sup>

The ideal approach to quality measurement incorporates structure, process, and outcome dimensions of quality and utilizes indicators that are valid, reliable, and easy to collect.<sup>15</sup> Rigorous development of potential quality of care measures requires establishing that the measure has (1) face validity—the perception that the measure actually reflects better or worse care; (2) construct validity—evidence that quality as measured



Table 1 - Predictors of surfactant use in cohort 1 (n=3,633)\*

	Odds Ratio	95% CI	p-value
<b>PATIENT-LEVEL PREDICTORS*</b>			
<b>Gestational age</b>			
30 weeks (n=621)	Reference		
31 weeks (n=620)	0.73	0.57-0.95	0.019
32 weeks (n=747)	0.68	0.53-0.87	0.002
33 weeks (n=715)	0.58	0.45-0.75	<0.001
34 weeks (n=930)	0.69	0.55-0.88	0.003
<b>Race†</b>			
Non-white (n=840)	Reference		
White (n=2,571)	1.22	1.02-1.47	0.03
<b>Gender</b>			
Female (n=1,535)	Reference		
Male (n=2,098)	1.34	1.15-1.57	<0.001
<b>Age at admission</b>			
Day of life 0 (n=3,107)	Reference		
Day of life 1 (n=526)	1.11	0.89-1.38	0.34
<b>Mode of respiratory support (first 48 hrs)</b>			
NCPAP (n=672)	Reference		
Mechanical ventilation (n=2,961)	54.99	35.86-84.35	<0.001
<b>HOSPITAL-LEVEL PREDICTORS††</b>			
<b>Research involvement</b>			
Top 10 hospital based on NIH total awards to children's hospitals	1.48	0.98-2.25	0.065
<b>Surgical volume</b>			
≥ 29% (median) of admissions to the NICU classified as surgical	1.58	0.79-3.16	0.193
<b>Payer mix</b>			
≥ 45% (median) of admissions to the hospital paid by Medicaid	0.80	0.40-1.61	0.532
<b>Patient volume</b>			
≥ 45 (median) Annual ELBW Admissions	1.80	1.02-3.19	0.042

NCPAP= nasal continuous positive airway pressure, NIH=National Institutes of Health; NICU=neonatal intensive care unit; ELBW=extremely low birth weight

\*Model includes patient-level variables listed in the table plus hospital fixed effects

†Model includes a term for missing race (n=222)

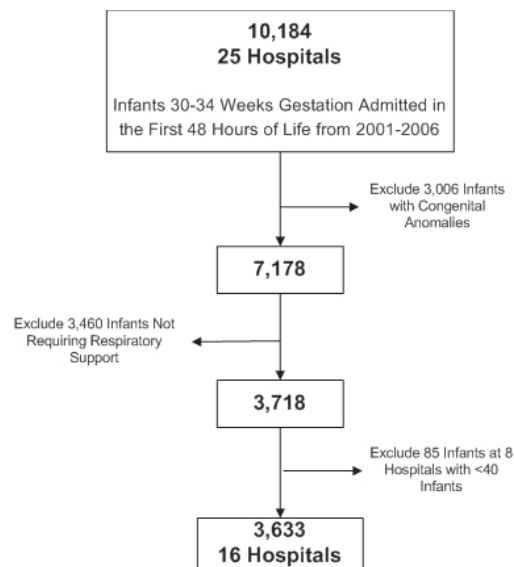
††Model includes patient-level variables listed in the table plus hospital characteristics added individually

by the proposed metric is consistent with quality when measured by other metrics; and, (3) stability over time. It also requires that the proposed metric be adequately measured with available data sources.

We aimed to assess whether surfactant use in infants 30 to 34 weeks' gestation with RDS is a valid measure of neonatal intensive care unit quality of care. Face validity was established by identifying support for this process in the medical literature and recommendations from professional organizations.<sup>9-11</sup> The objective of this study was to determine whether significant variation exists in the use of surfactant among infants 30 to 34 weeks' gestation across hospitals and to test the construct validity of surfactant use as a quality measure by identifying characteristics associated with higher rates of use and comparing ratings with two measures of quality—volume of admissions<sup>16-18</sup> and in-hospital mortality.<sup>16,17,19</sup>

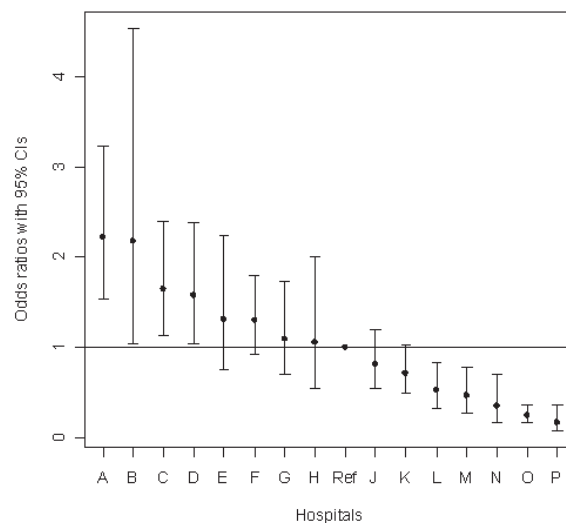
## Methods

**Data source:** Data were obtained from the Pediatric Health Information Systems (PHIS) database developed by the Child Health Corporation of America, a business alliance of freestanding, children's hospitals. PHIS contains data from 40 not-for-profit, tertiary care United States children's hospitals. This database contains demographic information, diagnosis and procedure codes (recorded using the International Classification of Diseases, 9<sup>th</sup> Revision, Clinical Modification (ICD-9-CM) format) and billed transaction and utilization data which are mapped to standardized Clinical Transaction Classification (CTC) codes. The database also contains all-patient refined diagnosis-related groups (APR-DRGs, version 15) and their associated birth weight groupings, as determined from patients' diagnosis and procedure codes and submitted birth weight (if available) using 3M proprietary software.



**Figure 1.** Inclusion and exclusion criteria applied to identify the study population. This figure displays how inclusion and exclusion criteria were applied to identify the study population. Prior to obtaining data from PHIS, 11 hospitals that do not submit gestational age information were excluded. From the initial study population of infants 30 to 34 weeks gestation admitted in the first 48 hours of life, exclusion criteria were applied sequentially.

**Study population:** The study cohort consisted of infants born at 30 to 34 weeks gestation with RDS, admitted between January 1, 2001 and March 31, 2006 to a hospital participating in the PHIS database. We defined RDS as requiring respiratory support with nasal continuous positive airway pressure (NCPAP) or mechanical ventilation (MV) in the first 48 hours of life, as determined from billing CTC codes and ICD-9-CM procedure codes. We chose to use a clinical definition of RDS instead of the ICD-9-CM diagnosis code (ICD-9-CM 769) in our primary analysis because assignment of the ICD-9-CM code is done retrospectively and may be biased by whether an infant



**Figure 2.** Adjusted hospital odds of receiving surfactant relative to reference hospital. This figure displays the hospital's adjusted odds ratio and associated 95% confidence interval (95% CI) of receiving surfactant relative to reference hospital defined as having the median adjusted rate of surfactant. After adjusting for patient characteristics, five hospitals had significantly decreased odds and four hospitals had significantly increased odds of giving surfactant, compared to the median hospital. After Bonferroni correction for multiple comparisons ( $p \leq 0.05/16 = 0.003$ ), 4 hospitals remained significantly different than the reference hospital.

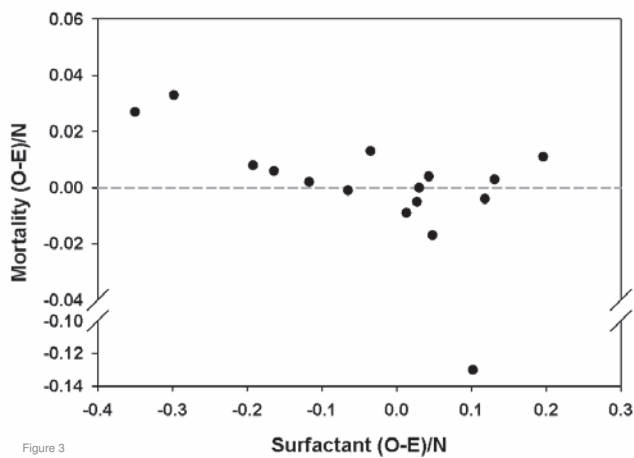


Figure 3

**Figure 3.** Association between hospital adjusted rates [(O-E)/N] for surfactant use and mortality. This scatter plot displays hospital adjusted rates [(O-E)/N] of surfactant use on the x-axis and hospital adjusted rates of mortality [(O-E)/N] on the y-axis (note break in y-axis). Although there was an outlier hospital, the overall trend in the plot is consistent with an association between decreasing mortality and increasing surfactant use (Kendall's tau correlation coefficient of 0.37,  $p=0.051$ ).

received surfactant. Additionally, the ICD-9-CM code for RDS has never been specifically validated and it is likely susceptible to coding errors because it requires significant judgment by data abstractors. We excluded infants admitted at >48 hours of life, who would be outside the treatment window for surfactant, and infants with congenital anomalies. We included data only from hospitals that submitted gestational age information. Hospitals that did not submit gestational age were similar to hospitals that did with regard to number of staffed beds, average daily census, and population of the surrounding city. We also included only those hospitals that submitted both billing and clinical data to PHIS. Hospitals with <40 eligible infants in the study period were excluded to minimize unstable estimates of the outcome in small centers. Figure 1 describes how the exclusion and inclusion criteria were applied to obtain the final study population.

**Data quality and missing data:** PHIS data are warehoused by a third-party vendor (previously Solucient, Ann Arbor, MI) which loads and processes data submitted by the hospitals. The warehouse partner applies 175 audits to each patient record. Submissions that do not meet the error thresholds are rejected. For example, neonate specific audits include identifying inconsistencies in typical length of stay (LOS) for a given birth weight group (i.e. LOS < 45 days for infant 600-749 grams) and identifying potential misclassifications of preterm and full term infants (i.e. BW < 2500 grams for a full term infant and BW > 2500 grams for a preterm infant). The hospital must correct the errors, resubmit the data, and meet the threshold before the data is included in PHIS.

A majority of the variables had missing data in <5% of observations. Race information was missing for 6% of patients. Among the population used to measure in-hospital mortality rates, 7.5% of patients had a gestational age that was determined to be inaccurate (<22 weeks or >43 weeks) or was missing. Patients with missing data were included in all analyses with variables coded in the regression models as absent (reference), present, and missing. Sensitivity analyses to the missing data were carried out for several aspects of the data analysis using imputed data and the results did not vary substantively from those presented here.

**Table 2 - Mean (O-E)/N for hospital surfactant use and death**

Hospital	Surfactant use	Death
	Mean (95% CI) p-value	Mean (95% CI) p-value
A	0.102 (0.082,0.122) <0.001*	-0.130 (-0.166,-0.092) <0.001*
B	0.196 (0.079,0.308) 0.010	0.011 (-0.004, 0.026) 0.219
C	0.131 (0.088,0.173) <0.001*	0.003 (-0.006,0.012) 0.573
D	0.118 (0.065,0.172) <0.001*	-0.004 (-0.014,0.006) 0.496
E	0.030 (-0.020,0.082) 0.312	0.00 (-0.012,0.011) 0.999
F	0.048 (0.026,0.071) <0.001*	-0.017 (-0.021,-0.013) <0.001*
G	0.043 (-0.031,0.114) 0.319	0.004 (-0.009,0.017) 0.534
H	0.027 (-0.086,0.137) 0.700	-0.005 (-0.024,0.015) 0.712
I	0.013 (-0.038,0.064) 0.659	-0.009 (-0.018,0.001) 0.129
J	-0.035 (-0.087,0.016) 0.265	0.013 (0.004,0.022) 0.001*
K	-0.065 (-0.113,-0.018) 0.020	-0.001 (-0.010,0.008) 0.845
L	-0.117 (-0.177,-0.057) 0.001*	0.002 (-0.008,0.011) 0.771
M	-0.164 (-0.240,-0.087) <0.001*	0.006 (-0.010,0.022) 0.536
N	-0.192 (-0.269,-0.111) <0.001*	0.008 (-0.006,0.023) 0.472
O	-0.298 (-0.337,-0.258) <0.001*	0.033 (0.023,0.044) <0.001*
P	-0.350 (-0.436,-0.260) <0.001*	0.027 (0.004,0.051) 0.041

\*significant with  $p \leq 0.05$  after Bonferroni correction ( $p \leq 0.05/16 = 0.003$ )

**Outcome of interest:** The primary outcome measure was receipt of surfactant within the first 48 hours of life. Surfactant use was identified by presence of an appropriate CTC code for any surfactant (i.e. lung surfactant unspecified, Beractant, synthetic lung surfactant, Calfactant, and Poractant alpha) in the pharmacy billing data. Only surfactant charges with a day of service within the first 48 hours of the infant's life were included.

**Hospital identifying characteristics:** Hospital factors of interest were the number of annual extremely low birth weight (ELBW) admissions to the NICU, percent Medicaid admissions to the hospital, amount of National Institutes of Health (NIH) research funding, and percent of admissions to the neonatal intensive care unit (NICU) with a principal surgical diagnosis. These variables were calculated for the most recent full year in the database (2005). ELBW admissions were defined using APR-DRG birth weight groupings. Amount of NIH research funding was obtained from the National Association of Children's Hospitals and Related Institutions for the year 2005.

**Hospital measures used to test construct validity:** The measure of volume of admissions used to test construct validity was determined as described above. We also aimed to test construct validity by comparing hospital rates of surfactant use with overall in-hospital mortality rates. This analysis is not intended to make a causal link between surfactant use and mortality at the patient-level but to examine whether rankings based on surfactant use are similar to rankings based on overall in-hospital mortality rates at the hospital-level. Overall NICU rates of mortality were determined using a second cohort of infants from the same hospitals which consisted of 24,421 neonates (any gestational age) admitted to a participating PHIS

NICU within 24 hours of birth during the same study period. This second cohort was necessary to provide the correct population for measuring overall in-hospital NICU mortality as an outcome measure of quality. We excluded five patients who lacked a recorded ICD-9-CM procedure or diagnosis code. Physiologic measures of severity of illness were unavailable in the PHIS database and risk adjustment models have not specifically been validated for use with this database. Therefore, we used demographic and clinical variables to control for differences in case-mix across hospitals when calculating adjusted rates of surfactant use and mortality as in previous studies.<sup>16,20</sup> The variables available to control for case-mix in our analyses (a subset of the variables included in previous studies) included gender, presence of any congenital anomaly, race, gestational age, and birth weight <10<sup>th</sup> percentile for gestational age.

**Statistical analysis:** Analyses were carried out using Stata 9 (College Station, TX); hypothesis tests were two-sided and used a Type I error rate of 0.05. Odds ratios (OR) are presented with their 95% confidence intervals (CI). Unless the model included individual hospitals as fixed effects, we used modified Huber-White sandwich estimators to adjust the standard error estimates in the regression models for possible correlations among patients from the same hospital.<sup>21</sup>

**Variation in surfactant use and hospital characteristics associated with use:** We built a patient-level logistic regression model for the study population that predicted surfactant use as a function of patient level variables (i.e. gestational age, race, gender, day of life on admission, and mode of ventilation). Indicator variables for specific hospitals were added to the model to estimate odds of surfactant use for each hospital relative to the hospital with the median rate of surfactant use (hospital I), after adjustment for patient characteristics.

**Comparison with other quality measures—construct validity:** We tested the construct validity of surfactant use as a measure of quality by (1) examining the association between surfactant use and hospital characteristics, specifically volume of admissions to the NICU (described in previous section), and (2) comparing adjusted hospital rates of surfactant use with adjusted hospital mortality rates. For the first test, we examined the coefficient of each hospital characteristic after individually adding the hospital-level characteristic to the patient-level model. For the second test of validity, using the population of patients of all gestational ages admitted in the first 24 hours of life, we built a logistic regression model to predict the odds of in-hospital mortality including covariates to adjust for case-mix (described in previous section). Using the logistic regression model to estimate the adjusted expected number of patient deaths (E) for each hospital, we calculated an (O-E)/N statistic for each hospital, where O was the observed number of events (deaths) at a hospital and N was the number of patients at the hospital.<sup>22</sup> We also calculated the (O-E)/N statistics for surfactant use at each hospital using the same methodology. This statistic reflects the excess or reduction in rate of surfactant use (or mortality) of a given hospital compared to an “average” hospital with the same mixture of patient characteristics. A test of whether the observed and expected rates differed was calculated using methods described by Haberman.<sup>23</sup> In addition, as a confirmatory analysis, we used bootstrap techniques<sup>24</sup> to obtain a mean (O-E)/N and 95% confidence interval for each hospital. The association between adjusted hospital mortality rates and adjusted hospital rates of surfactant use was assessed using Kendall’s tau

probability of concordance (which is calculated by the formula  $1 + \tau/2$ ) and the Kendall’s tau correlation coefficient.<sup>25</sup> The probability of concordance provides the probability that if a hospital is ranked higher on surfactant use, it will also have a better (lower) adjusted mortality rate.

**Sensitivity analyses:** In order to test whether variation in the odds of surfactant use among hospitals was robust to changes in the definition of RDS, we performed a sensitivity analysis defining RDS with the ICD-9-CM code for respiratory distress syndrome (ICD-9-CM 769) as opposed to the clinically derived definition of requiring ventilatory support (NCPAP or MV) in the first 48 hours of life. Additionally, to examine variation in the patient population specifically targeted by the American Academy of Pediatrics<sup>10</sup> for evidence based surfactant (intubated infants with RDS) and to examine the possible effect of receiving surfactant prior to transfer, we performed a sensitivity analysis examining only the cohort of infants admitted within 24 hours of birth who required mechanical ventilation.

## Results

**Variation in rates of surfactant use:** A total of 3,633 infants from 16 hospitals were included in the study population. Mean gestational age was  $32.2 \pm 1.4$  weeks. A majority of patients were male (57.8%) and of white race (70.8%). Overall, 46% of these patients received surfactant. Unadjusted rates of surfactant use among hospitals ranged from 18.9% to 71.4%. Among the 2,961 (81.5%) patients on mechanical ventilation during the first 48 hours of life, 55.6% received surfactant. Seventy-eight percent had an ICD-9-CM diagnosis code for RDS. Other diagnoses included congenital pneumonia (2.3%), meconium aspiration (0.2%), transient tachypnea of the newborn (8.6%), and severe birth asphyxia (0.7%). Of the included hospitals, 15 (94%) were academic centers and 14 (88%) were located in a city with a population >1 million.

Multivariate models indicated that gestational age, race, and gender were significantly associated with surfactant use (Table 1). Requiring mechanical ventilation sometime during the first 48 hours of life, compared to requiring only NCPAP, was most strongly associated with receipt of surfactant (OR 55, 95% CI 36–84). Receipt of surfactant was independent of whether the infant was admitted in the first 24 hours of life (day 0) or in the second 24 hours of life (day 1).

After adjusting for patient characteristics, five hospitals had significantly decreased odds and four hospitals had significantly increased odds of giving surfactant, compared to the median hospital (Figure 2). Odds ratios varied from as much as 2.2 (95% CI 1.53–3.23) times greater to 5.9 (95% CI 2.72–12.3) times less than the median hospital ( $p \leq 0.001$ ).

Among the 2,465 patients admitted within 24 hours of birth who required mechanical ventilation, unadjusted rates of surfactant use ranged from 19.2% to 76.3% across hospitals. Additionally, significant variation in adjusted surfactant use persisted in 7 of the 9 hospitals that were significant in the original analysis (Hospitals A, B, L, M, N, O, and P). Significant hospital variation in surfactant use was also found when the cohort was restricted to infants with an ICD-9-CM diagnosis code for RDS.

**Construct validity:** Among hospital-level characteristics, patient volume was significantly associated with variation in receipt of surfactant, while involvement in research approached



significance (Table 1). NICU surgical volume and hospital payer mix were not associated with surfactant use.

We compared adjusted hospital rates of surfactant use with adjusted in-hospital mortality rates. The mean bootstrap (O-E)/N values for surfactant use and death and the Haberman p-values for each hospital are shown in Table 2. The association between hospital surfactant use (measured by the (O-E)/N statistic for surfactant) and in-hospital NICU mortality (measured by the (O-E)/N statistic for death) is shown in Figure 3. The overall trend in the plot was consistent with an association between decreasing hospital mortality rates and increasing hospital rates of surfactant use (Kendall's tau correlation coefficient of 0.37, implying a probability of concordance of 0.69,  $p = 0.051$ ). This plot shows one outlier hospital with very low mortality rates. As Kendall's tau is rank-based and robust to outliers, the observed trend was unlikely to be driven by this outlier. We also found a statistically significant correlation between adjusted in-hospital NICU mortality rates and adjusted hospital rates of surfactant use among the population of infants requiring mechanical ventilation (Kendall's tau correlation coefficient of 0.38, also implying a probability of concordance of 0.69,  $p = 0.047$ ).

## Discussion

Healthcare providers strive to provide high quality care to their patients. However, in order to determine whether we are actually providing outstanding care, quality measures that are valid, reliable, and easy to collect are needed. We attempted to demonstrate that surfactant use in infants 30 to 34 weeks gestation with RDS may be a useful process measure of hospital quality.

Surfactant use in moderately preterm infants with RDS has the potential to be an ideal quality indicator if it can be accurately measured and can be shown to be a valid measure of quality. The best processes to use as quality indicators are those care practices with strong face validity and evidence linking them to improved patient outcomes. Although there are very few evidence-based therapies in neonatology, the efficacy of surfactant therapy for RDS has been proven in multiple clinical trials and a recent American Academy of Pediatrics report states that surfactant should be given to intubated infants with RDS regardless of exposure to antenatal steroids or gestational age<sup>10</sup>

In an effort to establish the construct validity of surfactant use in infants 30 to 34 weeks' gestation with RDS, we have shown significant variation in rates of surfactant use across hospitals and that hospital surfactant use was associated with variation in two of the most commonly used measures of neonatal quality—volume of admissions<sup>16-18</sup> and in-hospital mortality.<sup>17,19</sup> These findings are consistent with other examinations of variation in care practices published in the literature. For example, Horbar et al. documented variation in the use of early surfactant among VLBW infants similar to the variation we observed in larger preterm infants with RDS.<sup>13</sup> Additionally, our finding that hospital rates of surfactant use are associated with NICU volume of admissions is consistent with previous reports demonstrating a relationship between NICU volume of admissions and improved mortality.<sup>16,17</sup> While these results are encouraging, limitations in adequate measurement of this quality metric including defining RDS using administrative data, adequately adjusting for severity of illness, and accounting for care received prior to transfer preclude us from establishing the validity of this measure as a marker of neonatal quality of care. Additionally, this study did

not attempt to demonstrate the stability of the proposed quality measure over time.

Process measures require accurate identification of the appropriate eligible patient population. Identifying patients with RDS who are eligible for surfactant treatment was particularly challenging using administrative data. The RDS definition used in this study included infants requiring either NCPAP or MV in the first 48 hours of life. We believe this is a reasonable, practical definition for a clinical condition whose definition has varied even across clinical trials of surfactant therapy.<sup>4-6</sup> The definition included both NCPAP and MV in an effort to eliminate the effects of practice variation in ventilatory management across hospitals because the same infant, with the same severity of RDS, may be treated with NCPAP at one center and with MV at another center. However, in doing so, the denominator of eligible patients included some infants who could be successfully managed on NCPAP and some with more mild RDS who might not require surfactant treatment. The fact that there was still significant variation among hospitals in the use of surfactant when we used the ICD-9-CM diagnosis code to identify infants with RDS and when we restricted the population to only those infants requiring mechanical ventilation suggests that true variation exists. However, we acknowledge that there is a potential that systematic differences in RDS severity across hospitals or more liberal use of NCPAP in some centers could explain some of the variation in surfactant rates seen across hospitals. Future efforts to develop process measures in neonatology should focus on care practices with a clear and well-defined eligible patient population.

When the eligible patient population can be defined appropriately, process measures are typically insensitive to differences in case mix and severity of illness.<sup>1,26-28</sup> However, outcome measures of quality such as rates of in-hospital mortality (as used in this study for testing construct validity) require adequate risk adjustment to allow for fair and accurate comparisons across hospitals.<sup>27,29-32</sup> Administrative data is the most accessible comparative database for examining all patients admitted to a hospital and therefore is an important source of data for quality measurement.<sup>33</sup> However, administrative data sets often lack the richness of clinical data sources and they do not typically include physiologic measures of illness severity that can be used for adjustment when making comparisons across hospitals. While it is clear that physiologic measures of illness severity can provide a more nuanced adjustment for differences in case-mix related to illness severity, it is unclear how much these measures add or subtract to adjustments made using demographic and clinical variables as done commonly in other studies of variation in care.<sup>16,20</sup> The variables used to adjust for differences in case-mix when measuring surfactant use and in-hospital mortality in this study included an available subset of the demographic variables used in other studies. This specific combination of variables may not have fully accounted for differences in case-mix across hospitals and for differences in severity of illness; therefore, some of the variation we observed may be attributed to residual differences in case mix that were unaccounted for by our adjustment model. Future efforts to use administrative data to measure neonatal quality will need to first focus on developing valid risk adjustment models. More refined neonatal risk adjustment models are currently under development for use with the PHIS database (personal communication Matt Hall, CHCA).

Many neonatal quality measures are complicated by the impact of patient transfers between hospitals, which is a common occurrence in neonatal and perinatal care.<sup>15</sup> For example, development of valid measures of antenatal steroid use in eligible pregnant women is complicated by the fact that steroids may be given in multiple settings including outpatient clinics and referring hospitals. Measuring surfactant use in infants with RDS is similarly complicated. We do not have information on whether infants received surfactant at an outside hospital prior to transfer. In both our initial analysis and in sensitivity analyses, results were not affected by the day of life when the infant was admitted, making it less likely that receipt of surfactant at an outside hospital influenced whether the infant was truly eligible for surfactant. However, it is possible that variation in surfactant use across hospitals actually reflects differences in the care provided before transfer, instead of differences in the quality of care provided by the accepting facility. Future efforts to develop neonatal process measures of quality will likely need to focus on aspects of care that clearly occur at a single location or on developing accurate ways to assess and attribute care provided across multiple locations.

The hospitals that submit data to PHIS are mainly academic children's hospitals. Academic hospitals may vary in their quality of care compared to non-academic hospitals. In addition, we excluded centers with <40 eligible infants in the study period. These smaller NICUs may be less likely to provide high quality care compared to larger NICUs.<sup>16-18</sup> Therefore, additional efforts are needed to generalize these results and to understand how potential quality measures perform in non-academic or smaller NICUs.

## Conclusions

Our study was among the first to use administrative data to examine a process measure reflecting neonatal quality of care. While results were encouraging, challenges defining RDS using administrative data, ensuring adequate risk adjustment, and accounting for care received prior to transfer, did not allow us to draw definitive conclusions about the suitability of rates of surfactant use in infants 30 to 34 weeks' gestation with RDS as a quality indicator. More studies aimed at developing valid and reliable quality measures are needed in order to provide neonatologists with tools to understand and improve the care they provide.

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